National Clinical Guideline Centre

Chronic kidney disease (partial update)

Early identification and management of chronic kidney disease in adults in primary and secondary care

Guideline appendices A to R
July 2014

This guideline was updated and merged with NICE guidelines on managing hyperphosphateamia (CG157) and managing anaemia in CKD (NG8) in 2021. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021.

See the chronic kidney disease guideline on the NICE website for the guideline recommendations.

Final version

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
The Royal College of Surgeons of England
RCGP Royal College of General Practitioners
Royal College of Nursing
NICE accredited www.nice.org.uk/accreditation

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding

National Institute for Health and Care Excellence

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Appendix A: Scope

A.1 Scope from 2014 guideline

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care.

1.1 Short title

Chronic kidney disease.

2 The remit

This is a partial update of 'Chronic kidney disease' (NICE clinical guideline 73). See section 4.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

3 Clinical need for the guideline

3.1 Epidemiology

The classification of chronic kidney disease (CKD) developed by the Kidney Disease Outcome Quality Initiative (KDOQI) in 2002 provided a research focus for the last decade which has greatly improved understanding of CKD, its complications and the impact of CKD on healthcare resources.

CKD has been defined as evidence of reduced estimated glomerular filtration rate (eGFR) and/or structural or functional abnormalities other than GFR, sustained for at least 3 months. The early detection of CKD in England and Wales has been facilitated by the implementation of routine reporting of eGFR nationally, introduction of CKD indicators in the Quality and Outcomes Framework, increased awareness and education through guideline development and implementation, and local awareness-raising initiatives.

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The KDOQI classification defines five stages of CKD using a reduction in GFR and the presence of other markers of kidney damage, such as albuminuria or haematuria. Normal kidney function is defined as an eGFR ≥ 90 ml/min/1.73 m^2 with no other evidence of kidney damage. This classification was included in the previous Chronic kidney disease guideline (NICE clinical guideline 73) but stage 3 CKD was subdivided into 3A (GFR 45-59 ml/min/1.73 m^2) and 3B (GFR 30-44 ml/min/1.73 m^2), which has been now adopted internationally. The suffix 'p' in all stages to denote significant proteinuria was also introduced in the previous version of this guideline (Table 1).

Table 1: NICE CKD classification

Stage	eGFR (ml/min/1.73 m^2)	Description	Qualifier
1	≥ 90	Kidney damage, normal or increased GFR	Kidney damage (presence of structural abnormalities and/or persistent haematuria, proteinuria or microalbuminuria) for ≥ 3 months
2	60-89	Kidney damage, mildly reduced GFR	
3A	45-59	Moderately reduced GFR ± other evidence of kidney damage	GFR < 60 ml/min for ≥ 3 months ± kidney damage
3B	30-44		
4	15-29	Severely reduced GFR ± other evidence of kidney damage	
5	< 15	Established kidney failure	

Use the suffix (p) to denote the presence of significant proteinuria when staging CKD (albumin:creatinine ratio (ACR) ≥ 30 mg/mmol, or protein:creatinine ratio (PCR) ≥ 50 mg/mmol)

CKD is recognised as a global public health problem. Adult (age 18 years and older) prevalence studies from the USA and Norway show a broadly similar prevalence of around 10-13%. In the UK, stage 3-5 CKD, an eGFR less than 60 mL/min/1.73 m^2, has been widely used in prevalence estimates. The two largest studies, using different methodologies, reported an adult prevalence of CKD stage 3-5 in the general population of between 6.1 to 8.5%. The only study reporting overall adult prevalence of CKD in the UK comes from the Health Survey for England 2009 (a much smaller study in terms of number of participants but a representative population). Male prevalence of CKD was 14% and female 13%. In keeping with other studies the prevalence rose with increasing age, rising to 44% of men and 43% of women aged 75 years and over. Although the prevalence of end-stage renal disease is known to be increased in certain minority ethnic groups, the prevalence of

CKD does not differ by ethnicity. Age, hypertension and diabetes are key predictors of new-onset CKD.

The main risk associated with CKD is cardiovascular morbidity and mortality. Other important complications include those related to decreased GFR, acute kidney injury, infection, cognitive impairment, impaired physical function and progression of kidney disease. Complications may occur at any stage, often leading to death without progression to kidney failure. Complications may also arise from adverse effects of interventions to prevent or treat the disease and associated comorbidity. The risk for any adverse outcome increases with lower GFR and is multiplied by co-existent proteinuria.

The goals of early identification and management of CKD are to alleviate the risk of associated adverse outcomes and prevent progression and complications, therefore improving patient outcomes and reducing the impact of CKD on healthcare resources.

3.2 Current practice

Implementation of the evidence-based Chronic kidney disease guideline (NICE clinical guideline 73) has significantly improved identification of CKD, and increased awareness and understanding of the potential associated adverse outcomes. This required the development, implementation and integration of new policies, models and pathways of care. CKD has gone from an under-recognised condition in primary care prior to 2006, to one where those affected are recorded in disease registers and increasingly managed in accordance with evidence-based guidance.

CKD indicators were introduced in the primary care Quality and Outcomes Framework (QOF) in April 2006. These stated a requirement for primary care to produce a register of adults with stage 3-5 CKD, to measure and record blood pressure annually, and to record the percentage of people with CKD, hypertension and proteinuria on treatment with angiotensin-modulating drugs. The CKD indicators have been modified and updated in successive years, and from April 2009, include the percentage of patients on the CKD register with urine albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR) measures recorded within the previous 15 months (see Appendix, Table 2).

In the QOF Framework report for 2010/11, 8245 general practices in England are included in the published results, covering almost 100% of registered patients in

England. Ascertainment of CKD stage 3-5 in adults aged 18 and older has improved from 2.4% of the population, immediately following introduction of CKD indicators, to 4.3% in the latest report. Nevertheless, considerable variation in practice still occurs and ascertainment is not yet reaching the prevalence expected from epidemiological study. Lower socioeconomic status is associated with late referral and more severe CKD at time of presentation.

Definition, and recognition, of progression of CKD are areas of uncertainty. Practitioners will commonly have to decide whether or not a change in GFR is a true change based on a few recent GFR or serum creatinine measurements. Although this may be straightforward in those who follow a linear pattern of progression over time these people are in the minority. In many people with CKD non-linear patterns and extended periods of non-progression are common. Whatever the pattern of progression, there will be time-varying risk factors such as blood pressure control, medical events and medicines management that affect a person's risk of progression. For example, episodes of acute kidney injury are associated with increased likelihood of progression of existing CKD and with subsequent development of new-onset CKD.

Improved recognition of CKD has seen the late referral of patients with end-stage kidney failure fall from over 30% to 19% in the latest UK Renal Registry Report, and in the past 4 years renal replacement therapy acceptance rates have been stable at 109 per million of the population. Nevertheless further improvements can be made.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 years and older)

b) Consideration will be given to the needs of subgroups:

- Older people (75 years and older)
- Black and minority ethnic people (BME) where these differ from the needs of the general population
- People at high risk of developing CKD (for example, people with: diabetes, hypertension, cardiovascular disease, or people recovering from acute kidney injury).

4.1.2 Groups that will not be covered

a) People receiving renal replacement therapy (RRT)

b) People with acute kidney injury and rapidly progressive glomerulonephritis

c) Children and young people under 18 years

d) Pregnant women.

4.2 Healthcare setting

a) Primary and secondary NHS healthcare, including referral to tertiary care.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

Areas from the original guideline that will be updated

Investigation of CKD:

a) Measurement of kidney function and markers of kidney damage, for example using creatinine-based and cystatin C-based equations.

b) Frequency of monitoring.

Classification and early identification:

c) Classification of CKD.

Self management:

d) Dietary interventions such as a low protein diet in people with CKD.

e) Effectiveness of self-management support systems for people with CKD including relevant information and support.

Blood pressure control:

f) The choice of renin-angiotensin-aldosterone system antagonists including aldosterone antagonists in people with CKD.

Reducing cardiovascular disease:

g) Efficacy and safety of antiplatelet and antithrombotic therapy (for example, aspirin, ticagrelor, clopidogrel, dabigatran and warfarin) in people with CKD.

Asymptomatic hyperuricaemia:

h) Uric acid lowering therapy in people with CKD.

Specific complications of CKD – renal bone disease:

i) Vitamin D supplementation in the management of renal bone disease in people with CKD.

Areas not in the original guideline that will be included in the update

j) The risk of developing CKD after an episode of acute kidney injury.

k) The management of acidosis with bicarbonate supplementation in people with CKD.

4.3.2 Clinical issues that will not be covered

Areas from the original guideline that will be not be updated

No new evidence has been identified to directly change the 2008 recommendations on:

a) Investigation of CKD: indications for renal ultrasound.

b) Defining progression of CKD and the risk factors associated with progression.

c) Blood pressure control: practicalities of treatment with ACE inhibitors/ARBs.

d) Managing isolated microscopic haematuria.

e) Specific complications of CKD: anaemia.

f) Information and support for people and their carers (except for that relating to self-management support systems).

Areas not covered by the original guideline or the update

a) The treatment of each of the specific causes of CKD, such as glomerular and tubulointerstitial disease, or nephrotic syndrome.

b) Management of pregnancy in women with CKD.

c) Management of anaemia in people with CKD.

d) Management of acute kidney injury in people with CKD.

4.4 Main outcomes

a) Mortality (all cause and cardiovascular).

b) Hospitalisation.

c) Cardiovascular disease.

d) Progression of CKD.

e) Complications of CKD.

f) Patient safety (serious adverse events).

g) Health-related quality of life.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of

the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in September 2012.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- Chronic kidney disease. NICE clinical guideline 73 (2008).

5.1.2 NICE guidance to be incorporated

None.

5.1.3 Other related NICE guidance

- Patient experience in adult NHS services. NICE quality standard (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Early identification and management of chronic kidney disease in adults. NICE commissioning guideline 37 (2012).
- End of life care for adults. NICE quality standard (2012).
- Chronic kidney disease. NICE review decision (2011).
- Hypertension. NICE clinical guideline 127 (2011).
- Peritoneal dialysis. NICE clinical guideline 125 (2011).
- Chronic kidney disease. NICE quality standard (2011).
- Diabetes in adults. NICE quality standard (2011).

- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011).
- Chronic heart failure. NICE clinical guideline 108 (2010).
- Prevention of cardiovascular disease. NICE public health guidance 25 (2010).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009).
- Febuxostat for the management of hyperuricaemia in people with gout. NICE technology appraisal 164 (2008).
- Type 2 diabetes. NICE clinical guideline 66, partially updated by CG87 (2008).
- Lipid modification. NICE clinical guideline 67 (2008).
- Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy. NICE technology appraisal 117 (2007).
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006).
- Type 1 diabetes. NICE clinical guideline 15 (2004).
- Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure. NICE technology appraisal 48 (2002).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Osteoporosis fragility fracture risk. NICE clinical guideline 146. Publication expected August 2012.
- Acute kidney injury. NICE clinical guideline. Publication expected August 2013.
- Type 1 diabetes (update). NICE clinical guideline. Publication expected July 2014.
- Type 2 diabetes (update). NICE clinical guideline. Publication date to be confirmed.
- Lipid modification (update). NICE clinical guideline. Publication date to be confirmed.
- Management of hyperphosphataemia. NICE clinical guideline. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'.
- 'The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

Appendix

Table 2: Quality and Outcomes Framework CKD Indicators, Points Available and Practice Underlying Achievement 2008-2011 (reproduced from: Stevens et al. NDT 2012)

Indicator	Points Available	Underlying Achievement (All Practices)		
		2008/2009	2009/2010	2010/2011
CKD 1: The practice can produce a register of patients aged 18 years and over with CKD (US National Kidney Foundation: Stage 3 to 5 CKD). (R)	6	(Ascertained CKD prevalence 4.1%)	(Ascertained CKD prevalence 4.3%)	(Ascertained CKD prevalence 4.3%)
CKD 2: The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months. (P)	6	97.5%	97.6%	97.5%
CKD 3: The percentage of patients on the CKD register in whom the last blood pressure reading, measured in the previous 15 months, is 140/85 or less. (IO)	11	73.3%	73.9%	74.2%
CKD 5: The percentage of patients on the CKD register with hypertension and proteinuria who are treated with an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) (unless a contraindication or side effects are recorded). (P-T-O)	9*	87.3%	91.8%	90.5%
CKD 6: The percentage of patients on the CKD register whose notes have a record of a urine albumin: creatinine ratio (or protein: creatinine ratio) test in the previous 15 months. (P)	6†	-	77.7%	82.2%

*increased from 4 points to 9 points in 2009; †introduced in 2009

R = register, P = process, IO = intermediate outcome, P-T-O = process linked to outcome

Appendix B: Declarations of interest

B.1 Guideline development group members (2014)

B.1.1 Paula D'Souza

Item declared	Date	Expiry	Classification	Action taken
Registration, travel and parking to attend BRS from Boehringher-Ingelheim.	May 2012	April 2013	Personal specific pecuniary	Declare and participate – standard, reasonable expenses
Talk by spouse at 'Diabetes and CKD', sponsored by Boeringer Ingelheim. Fee received.	12 September 2012 (declared 04-03-2013)	11 September 2013	Personal family specific pecuniary	Declare and withdraw from: Q10 (RAAS) GDG7 May 2013 and Q11 (AP/AC) GDG9 July 2013
Talk by spouse at 'CKD and its management in Primary Care'. Sponsored by Astra Zeneca. Fee received.	19 December 2012 (declared 04-03-2013)	18 December 2013	Personal family specific pecuniary	Declare and withdraw from: Q10 (RAAS) GDG7 May 2013 and Q11 GDG9 (AP / AC) July 2013
Attended a sponsored (Amgen) educational evening and dinner with spouse. No financial contribution to participants.	17 January 2013 (declared 04-03-2013)	16 January 2014	Personal specific and personal family specific	Declare and participate (Cinacalcet excluded from Q13)
Gave presentation to HCPs on CKD and its management in primary care, sponsored by Astra Zeneca; petrol expenses received.	03 April 2013	02 April 2014	Personal specific pecuniary	Declare and participate – standard, reasonable expenses
Will be attending the ERA (Istanbul) 18-21 May 2013; registration, economy flights and standard accommodation funded by Boeringer Ingelheim	18-21 May 2013	20 May 2014	Personal specific pecuniary	Declare and participate – standard, reasonable expenses

Item declared	Date	Expiry	Classification	Action taken
Attended a sponsored educational evening on CKD - MBD on June the 24th 2013. The event was sponsored by Amgen and Fresenius, however no financial reimbursement or meal was received.	24 June 2013	23 June 2014	Personal specific non-pecuniary	Declare and participate.
Attended an educational evening sponsored by Boeringer Ingelheim. This involved an educational talk followed by a meal (no alcohol). Event attended in October 2013.	28 April 2014	-	Personal specific pecuniary	Declare and participate – standard, reasonable expenses

B.1.2 Hugh Gallagher

Item declared	Date	Expiry	Classification	Action taken
Honoraria from Astra Zeneca for 2 GP lectures on the management of diabetes and renal disease.	24 November 2011 12 January 2012	11 January 2013	Personal specific pecuniary	None – conflict expired (Q10 / Q11 May and July 2013)
Participation in market research activities commissioned by unknown pharma company. Fee received.	4 February 2013	3 February 2014	Personal non-specific pecuniary	Declare and participate
Publication: Creatinine Fluctuation Has a Greater Effect than the Formula to Estimate Glomerular Filtration Rate on the Prevalence of Chronic Kidney Disease. de Lusignan S, Tomson C, Harris K, van Vlymen J, Gallagher H. Nephron Clin Pract. 2010 Aug 31;117(3):c213-c224.	2010	-	Personal non-pecuniary	Declare and participate
Publication: Telling the Truth: why disclosure matters in chronic kidney disease (editorial). Abdi Z, Gallagher	2012	-	Personal non-pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
H, O'Donoghue D. Br J Gen Pract. 2012 Apr;62(597):172-3.				

B.1.3 Kathryn Griffith

Item declared	Date	Expiry	Classification	Action taken
Involved in a project on Commissioning in Primary care developed by Virgo Health but funded by Roche	27-28 August 2011	26 August 2012	Personal specific pecuniary	None – conflict expired
Attended the ESC as a guest of MSD who paid for standard Euro-star ticket and 2 nights of accommodation.	14 September 2011	14 September 2012	Personal pecuniary	None – conflict expired
Spoke at educational meetings for primary care on advances in AF management & received an honorarium from Boehringer Ingelheim.	26 September 2011 and 13 October 2011	12 October 2012	Personal specific pecuniary	None – conflict expired
Chaired an advisory Board on AF for Boehringer Ingelheim & received travel expenses and an honorarium.	18 January 2012	17 January 2013	Personal specific pecuniary	None – conflict will have expired by GDG 4 (01-02-2013) when relevant Q11 (AP / AC) addressed
Involved in an educational session on AF for Pfizer & received an honorarium.	10 February 2012	9 February 2013	Personal specific pecuniary	Declare and withdraw from: Q11 (AP / AC) GDG 4 on 01-02-2013. Conflict expired by GDG 11 when Q11 readdressed
Attended a session on the AF Lifelines project for Pfizer & received an honorarium.	12 July 2012	11 July 2013	Personal specific pecuniary	Declare and withdraw from Q10 (RAAS) GDG 7 on 17-05-2013

Item declared	Date	Expiry	Classification	Action taken
Member of the Renal Association and British Renal Society CKD forum.	On-going		Personal non-pecuniary	Declare and participate Will not contribute to sending in RA or BRS stakeholder comments when the guideline consults (as will participate in answering these with the GDG)
Speaker at Meeting of the BMJ Masterclass on CKD in Primary Care. Fee and travel expenses paid by the BMJ.	13 September 2013	12 September 2014	Personal pecuniary non-specific (non- pharma)	Declare and participate
Senior Clinical Tutor for Bradford University PwSI Programme. Teaching on the CHD module on 14 September 2012, the Hypertension and Arrhythmia Management module on 15 February 2013 as well as examiner 21-22 February 2013. Fee, travel and accommodation paid.	September 2012 – February 2013	21 February 2013	Personal pecuniary non-specific (non- pharma)	Declare and participate
Speaker for Mediconf at Meeting on AF. Fee and travel expenses paid.	15 September 2012	14 September 2013	Personal pecuniary non-specific (non- pharma)	Declare and participate
Speaker for Pulse Medical Journal at meeting on AF. Fee and expenses paid.	26 September 2012	25 September 2013	Personal pecuniary non-specific (non- pharma)	Declare and participate
Speaker at meeting on AF in Leeds. Fee paid by Dr Adil Suleman.	13 October 2012	12 October 2013	Personal pecuniary non-specific (non- pharma)	Declare and participate
Speaker at Anaemia Nurse Specialist Association (ANSA) Meeting on Iron Deficiency in Primary Care. Fee and travel expenses paid.	9 November 2012	8 November 2013	Personal pecuniary non-specific (non- pharma)	Declare and participate
Speaker at meeting on Management of AF for the	5 December 2012	4 December 2013	Personal pecuniary non-	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
RCGP. Fee and expenses paid.			specific (non- pharma)	
Participation in Round Table Meeting 12 November 2012 to develop Supplement for British Journal of Cardiology on Management of Hypertension published in March 2013. Fee paid into practice (Unity Health). Standard travel expenses paid by Takeda.	12 November 2012	11 November 2013	Non-personal specific pecuniary and Personal specific pecuniary (standard, reasonable expenses)	Declare and participate
Speaker fee for meeting on Venous Thromboembolism arranged by Bayer. Fee paid into practice (Unity Health).	5 December 2012	4 December 2013	Non-personal pecuniary	Declare and participate
Speaker fee from WP Event Management for meeting on CKD, CVD and Diabetes. Fee paid into practice (Unity Health).	26 February 2013	25 February 2014	Non-personal pecuniary	Declare and participate
Member of the KDIGO CKD Guideline Update Group 2011-2012 with travel expenses paid by KDIGO and no other payment made.	2011-2012		Personal pecuniary	Declare and participate – standard, reasonable expenses
Attended the Renal Advisory Group meeting at the Department of Health. Travel and locum expenses paid.	8 October 2012	7 October 2013	Personal pecuniary	Declare and participate – standard, reasonable expenses
Attended the Primary Care Stroke Research Group meeting. Travel and locum expenses paid.	9 October 2012	8 October 2013	Personal pecuniary	Declare and participate – standard, reasonable expenses
Chair and Speaker at Meeting of Primary Care Cardiovascular Journal on CKD. Travel expenses and accommodation provided, no fee paid.	16-17 November 2012	16 November 2013	Personal pecuniary	Declare and participate – standard, reasonable expenses
Primary Care Clinical Lead for the WY Cardiovascular	January-February	19 February 2014	Personal non-pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
and Stroke Network. Talks on AF and Anticoagulation on 30 January, 5 February, 12 February and 20 February 2013. No fee.	2013			
Participation in the American College of Cardiology meeting (iACC) 9-11 March 2013. Travel, hotel and delegate registration paid by Boehringer Ingelheim (standard expenses only).	11 March 2013	10 March 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Speaker at Meeting on Atrial Fibrillation arranged by EH Medical Meetings. But sponsored by Bayer. Fee paid to CVGP the Society for GP with an interest in Cardiovascular disease.	7 September 2013	6 September 2014	Non-personal pecuniary	Declare and participate
Speaker at CVGP meeting in Cambridge sponsored by CVGP and accommodation provided by CVGP	14 September 2013	13 September 2014	Personal non-pecuniary	Declare and participate
Speaker at meeting in Birmingham on Atrial Fibrillation. Fee and travel expenses paid by Omnium Medical Meetings.	25 September 2013	24 September 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Speaker at BMJ Masterclass in Manchester with fee and travel paid by BMJ Education.	26 September 2013	25 September 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Speaker at Meeting in Bradford on Anticoagulation Choices for AF. Travel and fee paid by Leeds University Pharmacy Course.	2 October 2013	1 October 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Speaker at primary care meeting on Atrial Fibrillation. Fee paid to Unity Health by Boehringer Ingelheim.	8 October 2013	7 October 2014	Non-personal pecuniary	Declare and participate
Attended Northern Lights Meeting of CVGP which was sponsored by Pfizer but I paid for my own	14 October 2013	13 October 2014	Personal non-pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
refreshments and travel.				
Attended ACC in March 2014 with travel and accommodation sponsored by Boehringer Ingelheim.	28 April 2014	-	Personal pecuniary	Declare and participate – standard, reasonable expenses

B.1.4 Karen Jenkins

Item declared	Date	Expiry	Classification	Action taken
Consultancy work for TAKEDA - completed June 2012	Sept 2011 – June 2012	June 2013	Personal specific pecuniary	Declare and withdraw from Q10 (RAAS) GDG 7 on 17-05-2013
Participated in a training workshop for dieticians sponsored by Sanofi on pharmaceuticals. Reasonable travel expenses only.	5 December 2012	4 December 2013	Personal specific pecuniary	Declare and participate – standard, reasonable expenses
Attending annual ANSA conference; travel, registration and accommodation paid by ANSA	19 April 2013	18 April 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Chairing a session at British Renal Society (BRS) Conference; subject 'How CKD contributes to cardiovascular risk and improving patient outcomes. Attending the British Renal Society Conference as a member of the BRS council and CKD Strategy Group Chair. Travel, registration and accommodation paid by the BRS	13-15 May 2013	14 May 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Co-authored editorial for Journal of Renal Nursing entitled 'Patient self-care: are we getting the balance right?'; personal payment as a Consultant Editor for JRN.	04 April 2013	03 April 2014	Personal pecuniary	Declare and participate (non-healthcare industry related)

B.1.5 Paul Kendrew

Item declared	Date	Expiry	Classification	Action taken
Attended a talk and a dinner sponsored by Takeda at the British Transplant Society.	March 2013	Feb 2014	Personal specific pecuniary (dinner)	Declare and withdraw from Q10 (RAAS) GDG7 on 17-05-2013
Gave a talk at the Pharmacy Congress. Fee received, but not from a specific pharmaceutical company.	April 2013	March 2014	Personal non-specific pecuniary	Declare and participate
Gave a talk for the centre for postgraduate pharmacy education (CPPE) on chronic kidney disease.	May 2013	April 2014	Personal non-specific pecuniary	Declare and participate (non-pharma funding)

B.1.6 Ed Lamb

Item declared	Date	Expiry	Classification	Action taken
Papers: Carter JL, Stevens PE, Irving J, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. QJM 2011;104:839-847, doi: 10.1093/qjmed/hcr077 PMID: 21652537 Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for GFR in the era of creatinine standardization: a systematic review. Ann Int Med			Personal non-pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
2012;156:785-795 Sardiwal S, Gardham C, Coleman A, Stevens PE, Delaney MP, Lamb EJ. Bone-specific alkaline phosphatase concentrations are less variable than parathyroid hormone concentrations in stable hemodialysis patients. Kidney Int 2012; 82:100-105 Garrett G, Sardiwal S, Lamb EJ, Goldsmith DJA. PTH – A particularly tricky hormone: why measure it at all in kidney patients? Clin J Am Soc Nephrol 2012;7: accepted for publication 3rd January 2012 McTaggart MP, Newall RG, Pinnock RG, Stevens PE, Price CP, Lamb EJ. The diagnostic accuracy of a urine albumin-to-creatinine ratio point-of-care test for use in the detection of albuminuria. Am J Kidney Dis 2012;60:787-794 Lamb EJ, Miller WG. A decade after the KDOQI CKD guidelines - impact on clinical laboratories [editorial]. Am J Kidney Dis 2012;60:719-722 Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP, Farmer CKT, Irving J, O'Riordan SE, Dalton N, Lamb EJ. Accuracy of the MDRD				

Item declared	Date	Expiry	Classification	Action taken
(Modification of Diet in Renal Disease) Study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis 2013;61:57-66 Lamb EJ, McTaggart MP, Stevens PE. Counterpoint. Why ACR should replace PCR: it is not just about nephrologists. Annals Clinical Biochemistry. 2013, accepted for publication 7th November 2012 Lamb EJ, Levey AS, Stevens PE. Perspective. The Kidney Disease Improving Global Outcomes Guideline Update for Chronic Kidney Disease: evolution not revolution. Clin Chem 2013, Accepted for publication *Guideline Development group member:* Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–150				
Speaker invitations:				
Lamb EJ. Assessment of GFR and proteinuria: what have KDIGO changed? Oral presentation (invited speaker) at Focus 2012, National Meeting of the Association for Clinical Biochemistry, Liverpool, UK,	May 2012	April 2013	Personal non-specific pecuniary	Declare and participate – (non-pharma funding)

Item declared	Date	Expiry	Classification	Action taken
May 2012. Ann Clin Biochem 2012;49(suppl.1):8-9 *Funded by Association for Clinical Biochemistry and Laboratory Medicine (accommodation and travel).*				
Lamb EJ. KDIGO guideline for CKD: implications for the laboratory. Oral presentation (invited speaker) at Pathpoint 2012, congress of the Federation of South African Societies of Pathology and the Association of Pathologists of East, Central and Southern Africa, Cape Town, South Africa, September 2012. *Funded by South African Societies of Pathology (accommodation) and Association Association for Clinical Biochemistry and Laboratory Medicine (travel reimbursement only).*	September 2012	August 2013	Personal non-specific pecuniary	Declare and participate – (non-pharma funding)
Lamb EJ. Managing CKD-MBD using PTH: is it useful? Oral presentation (invited speaker) at Pathpoint 2012, congress of the Federation of South African Societies of Pathology and the Association of Pathologists of East, Central and Southern Africa, Cape Town, South Africa, September 2012. *Funded by South African Societies of Pathology (accommodation) and Association Association for Clinical Biochemistry and Laboratory Medicine (travel reimbursement only).*	September 2012	August 2013	Personal non-specific pecuniary	Declare and participate – (non-pharma funding)
Lamb EJ. Managing CKD-MBD using PTH: can we do better? Oral presentation (invited speaker) at joint meeting of the Scottish Renal Association and Scottish	November 2012	October 2013	Personal non-specific pecuniary	Declare and participate – (non-pharma funding)

Item declared	Date	Expiry	Classification	Action taken
Region of the Association for Clinical Biochemistry, Aberdeen, November 2012. *Funded by Scottish Renal Association (travel and accommodation).*				
Lamb EJ. Biomarkers of AKI – horizons. Oral presentation (invited speaker) at AKI Consensus Conference, Royal College of Physicians of Edinburgh, Edinburgh, UK, November 2012. *Funded by Royal College of Physicians of Edinburgh (travel and accommodation).*	November 2012	October 2013	Personal non-specific pecuniary	Declare and participate – (non-pharma funding)
Member of the original 2008 NICE CKD GDG and have defended the recommendations of that guideline at many public scientific and clinical meetings since.	2008		Personal non-pecuniary	Declare and participate
Lead applicant on: HTA Project: 11/103/01 - Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: an observational study in a multiethnic population.	Funding confirmed 25 February 2013		Non-personal, non-industry, pecuniary	Declare and participate
Invited to write an educational article for the BMJ on rational use of eGFR. No financial reimbursement.	Due to submit July 2013		Personal non-pecuniary	Declare and participate
Part of kidney research UK expert group working with 'Roche' to discuss opportunities to set up cohort studies to identify new biomarkers for CKD	21.06.13	20.06.14	Personal non-pecuniary specific	Declare and participate

B.1.7 Robert Lewis

Item declared	Date	Expiry	Classification	Action taken
Flight, accommodation and registration at 'Nephrology at the Edge', Cape Town. Financed by a cooperative of pharmaceutical companies.	23-26 March 2012	25 March 2013	Personal pecuniary	Declare and participate – standard reasonable expenses
Flight, accommodation and registration at American Society of Nephrology, San Diego, sponsored by Jansen Cilag Ltd.	31 Oct- 5 Nov 2012	4 November 2013	Personal pecuniary,	Declare and participate – standard, reasonable expenses
Author of a book "Chronic Kidney Disease – a Guide for the Non-Specialist" published by MK publishing in October 2012	October 2012	September 2013	Personal non-pecuniary	Declare and participate
Author of future article on CKD for the Primary care Journal of cardiovascular disease.	Declared 28 November 2012	27 November 2013	Personal pecuniary	Declare and participate
Author of a series of future articles for Pulse magazine on CKD	Declared 28 November 2012	27 November 2013	Personal non-pecuniary	Declare and participate
Attend European Renal Association 17th May 2013. Sponsorship from Jansen-Cilag includes standard expenses for travel, registration, accommodation and food.	17 May 2013	16 May 2014	Personal non-pecuniary	Declare and participate – standard, reasonable expenses
Travel and accommodation costs to speak at the Home Dialysis Symposium, Manchester October 3rd 2013. Honorarium may be paid, from a hospital endowment fund.	3rd October 2013	3rd October 2014	Personal pecuniary	Declare and participate

B.1.8 Fiona Loud

Item declared	Date	Expiry	Classification	Action taken
NIHR funded CKM (Conservative Kidney Management) OPPS – patient advisor (fee and travel expenses).	On-going		Personal pecuniary	Declare and participate - non-healthcare industry funding.
Health Foundation funded Closing the Gap (Patient education CKD in Primary Care) - patient and service team leader (fee and travel expenses).	Ends September 2012		Personal pecuniary	Declare and participate - non-healthcare industry funding.
City University Kidney Research Education Initiative funded by British Kidney Patients Association (fee and travel expenses).	On-going		Personal pecuniary	Declare and participate - non-healthcare industry funding.
Attended a meeting with the Kidney Health for Life Coalition in Paris, discussing prevention and treatment of early CKD. Sponsored by Abbott, and fare paid by them (no fee received).	24 May 2012	23 May 2013	Personal pecuniary	Declare and participate – standard, reasonable expenses
Received a fee for project management work for World Kidney Day from the Kidney Alliance, set in June 2011 and not related to the amount raised. Non-pharma funding.	March 2012	February 2013	Personal pecuniary	Declare and participate – non-healthcare industry funding
Received a fee from Novartis for speaking to a group of transplant surgeons about immunosuppression from a patient viewpoint.	October 2011	October 2012	Personal specific pecuniary	None – conflict will have expired
The Kidney Alliance received funding for its World Kidney day activity in March 2012 from the following: Abbott, Amgen, Fresenius, Shire, NxStage, Takeda, Pfizer	March 2012	February 2013	Non-personal specific pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
Interview in March 2012 to a media company working for Shire, reflecting experiences as a kidney patient with regard to diet and medication. Personal fee and a donation to a local charity.	Fee 31 January 2013	30 January 2014	Personal specific pecuniary	Declare and withdraw from Q13 (Vit D) - Review debated at GDG3 in December 2012 (before COI declared). Withdraw from any further discussions of vitamin D from Jan 2013
Chairing conference run by 'SBK Healthcare' called Renal Service Change Management. Fee received.	3 December 2012	2 December 2013	Personal pecuniary non specific	Declare and participate
A fee from the Welsh CKD framework for training CKD and practice nurses in how to enable self-care. Reasonable expenses only paid.	28 September 2012	27 September 2013	Personal non-pecuniary	Declare and participate
Participation in a day's training in 'healthcare social marketing' in September 2012 from Roche Pharmaceuticals. Group event for health charities, event free to attend. Normal travel expenses only paid.	September 2012	October 2013	Personal pecuniary	Declare and participate – standard, reasonable expenses
The Kidney Alliance received funding for its 2013-2014 review of the National Service Framework from Takeda, Fresenius	October 2012	September 2013	Non-personal pecuniary	Declare and participate
Participation in 2 events funded by Abbott Healthcare towards the Kidney Health 2032 project (think-tank).	October 2012	September 2013	Personal non-pecuniary	Declare and participate
The Kidney Alliance received funding for its World Kidney day 2013 from the following: Amgen, Takeda, Fresenius	December 2012-February 2013	January 2014	Non-personal specific pecuniary	Declare and participate
Invited speaker (in March 2013) to a Fresenius	March 2013	February 2014	Personal non-specific	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
advisory board about changes in and impacts of NHS commissioning and optionally to listen to a discussion about a new phosphate binder (PA21). Received a fee.			pecuniary	
Author of part of a chapter of a new textbook on Renal Nursing (ed Nicola Thomas, publisher Wiley-Blackwell) about self-management to be published after September 2013. No fee.	Declared February 2013, published after Sept. 2013	-	Personal non-pecuniary	Declare and participate
Invited speaker at the BRS conference in mid-May about a) commissioning for patients in the NHSCB and b) What I would like my care to look like in the next 10 years. Expenses will be provided by the BRS.	Declared February 2013, conference mid-May 2013	April 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Co-applicant (patient representative) on HTA Project: 11/103/01 - Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: an observational study in a multiethnic population.	Funding confirmed 25 February 2013	-	Pecuniary (non-healthcare industry related) and neither personal nor non personal (no managerial responsibility for dept)	Declare and participate
Co-applicant for a £2M grant just awarded by the NIHR (non-pharma) for a multicentre study assessing the utility of cystatin C for CKD progression.	April 2013	-	Pecuniary (non-healthcare industry related) and neither personal nor non personal (no managerial responsibility for dept)	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
Speaking on Patient Decision Aids at ReMec (Renal Medicine, run by Central Manchester University Hospitals NHS Foundation Trust Hospital) meeting in Warrington; will receive travel expenses and speaker fee	25 April 2013	24 April 2014	Personal non-specific pecuniary	Declare and participate
Speaking at the British Renal Society on 'What I want my care to look like in 2023' and 'Commissioning – patient perspective on involvement to improve our service.' Travel, registration and accommodation paid by the British Renal Society.	15-16 May 2013	15 May 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Travel expenses from Amgen to go to annual renal Clinical Directors meeting to present on Kidney Health project April 2013. Travel and accommodation expenses from the International Society of Nephrology (ISN) to speak at their Nexus conference in Italy May 2013.	25 May 2014	-	Personal pecuniary	Declare and participate – standard, reasonable expenses

B.1.9 Shelagh O'Riordan

Item declared	Date	Expiry	Classification	Action taken
Co-author on: 1. Kilbride H, Eaglestone G, Knight S, Carter JC, Delaney MP, Farmer CKT, O'Riordan SE, Dalton N,	Accepted for publication 18 June 2012	-	Personal non-pecuniary specific	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
Stevens PE, Lamb EJ. Accuracy of the MDRD and CKD-EPI equations for estimation of GFR in the elderly. Am J Kidney Dis 2012;				
Investigator on HTA Project: 11/103/01 - Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: an observational study in a multiethnic population.	Funding confirmed 25 February 2013	-	Personal non-pecuniary specific	Declare and participate

B.1.10 Nicholas Palmer

Item declared	Date	Expiry	Classification	Action taken
Participation in a round table discussion on 3rd October on home haemodialysis, sponsored by Baxter (honorarium and hotel accommodation)	October 2012	October 2013	Personal pecuniary non-specific	Declare and participate
Participation in a conference on 3 December, run by SBK Healthcare, called 'Managing Improvement in Renal services'	October 2012		Personal non-pecuniary non-specific	Declare and participate
Participated in an advisory board meeting sponsored by Fresenius discussing the implications of the 'new' NHS on commissioning renal services; honorarium payment received.	18 March 2013	17 March 2013	Personal pecuniary non specific	Declare and participate
Participated in a World Kidney Day event for Sanofi raising awareness about CKD and transplantation	14 March 2013	13 March 2014	Personal non pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
amongst their staff. No payment received.				
I will be attending a Holiday Dialysis Conference in Barcelona, September 2013, my flights and accommodation will be paid for by the sponsors and organisers – Diaverum.	September 2013	September 2014	Personal pecuniary non-specific	Declare and participate
Presenting to the Associated Renal Industry (ARI) in December about 'NKF Patient Advocacy – it's role and value within the Renal Community'. No fee being paid.	December 2013	December 2014	Personal non-pecuniary	Declare and participate.

B.1.11 Paul Roderick

Item declared	Date	Expiry	Classification	Action taken
Member of the research team for a PFIZER funded study on wound infection epidemiology in GPRD	Ongoing		Non-personal pecuniary specific	Declare and participate
Author or co-author on: 1. Roderick PJ. Assessing the impact of chronic kidney disease on individuals and populations: use of relative and absolute measures. Nephrol Dial Transplant. 2012 Feb 29. [Epub ahead of print] 2. Roderick PJ. Chronic kidney disease in older people: a cause for concern? Nephrol Dial Transplant. 2011 Oct;26(10):3083-6.	Sept. 2012	-	Personal non-pecuniary specific	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
Epub 2011 Sep 13. 3. International Consortium for Blood Pressure Genome-Wide Association Studies; CARDIoGRAM consortium; CKDGen Consortium; KidneyGen Consortium; EchoGen consortium; CHARGE-HF consortium. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011 Sep 11;478(7367):103-9. doi: 10.1038/nature10405.				
Part of kidney research UK expert group working with 'Roche' to discuss opportunities to set up cohort studies to identify new biomarkers for CKD	21-06-2013	-	Personal non-pecuniary specific	Declare and participate

B.1.12 Paul Stevens (Chair)

Item declared	Date	Expiry	Classification	Action taken
Co-author on: 1. Kilbride H, Eaglestone G, Knight S, Carter JC, Delaney MP, Farmer CKT, O'Riordan SE, Dalton N, Stevens PE, Lamb EJ. Accuracy of the MDRD and CKD-EPI equations for estimation of GFR in the elderly. Am J Kidney Dis 2012; accepted for publication 18th June	Kilbride et al accepted for publication June 2012 Carter et al. October 2011	-	Personal specific non-pecuniary	Declare and participate

Item declared	Date	Expiry	Classification	Action taken
2. Carter JL, Stevens PE, Irving J, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. QJM 2011;104:839-847, doi: 10.1093/qjmed/hcr077 PMID: 21652537 (Non pecuniary).				
Co-Chair of KDIGO	On-going		Personal specific non-pecuniary	Declare and participate
Co-applicant on HTA Project: 11/103/01 - Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: an observational study in a multiethnic population.	Funding confirmed 25 February 2013		Non personal pecuniary (non-healthcare industry related)	Declare and participate (decision made by Guideline Lead and Clinical Director)
Co-applicant for a £2M grant just awarded by the NIHR (non-pharma) for a multicentre study assessing the utility of cystatin C for CKD progression.	March 2013	-	Non personal pecuniary specific (non-healthcare industry related)	Declare and participate (decision made by Guideline Lead and Clinical Director)
Invited speaker at a French Society of Nephrology meeting in Lyon; subject 'How to control the CKD workload'. Travel expenses and hotel accommodation sponsored by Hemotech (French dialysis company).	28 March 2013	27 March 2014	Personal non-specific pecuniary	Declare and participate – standard, reasonable expenses
Speaking at the British Renal Society (BRS); subject 'The BRS in the NICE era'. Travel, registration and accommodation paid by the BRS.	15 May 2013	14 May 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses
Speaking at the World Congress of Nephrology (Hong Kong); subject 'KDIGO – clinical practice guidelines for	01 June 2013	31 May 2014	Personal pecuniary	Declare and participate – standard, reasonable expenses

Item declared	Date	Expiry	Classification	Action taken
evaluation and management of CKD: research gaps from an international perspective'. Travel, registration and accommodation paid by the International Society of Nephrology.				
Invited to write an educational article for the BMJ on rational use of eGFR. No financial reimbursement.	Due to submit July 2013		Personal non-pecuniary	Declare and participate

B.2 Invited experts (2014)

Caroline Ashley (Attended GDG 7)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Campbell Cowan (Attended GDG 9)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Nervine El-Sherbini (Attended GDG 2)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Rob Henderson (Attended GDG 9)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Daniel Lasserson (Attended GDG 7)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Tom Kenny (Attended GDG 11)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

Pamela Young (Attended GDG 11)

Item declared	Date	Expiry	Classification	Action taken
Nothing declared				

B.3 Technical team members (2014)

Name	Personal pecuniary interest *	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
Caroline Blaine	Nil	Nil	Nil	Nil
Serena Carville	Nil	Nil	Nil	Nil
Lisbeth Hoeg-Jensen	Nil	Nil	Nil	Nil
Lilian Li	Nil	Nil	Nil	Nil
Jill Parnham	Nil	Nil	Commissions received from non pharma related international work	Nil
Sharon Swain	Nil	Nil	Nil	Nil
Richard Whittome	Nil	Nil	Nil	Nil
David Wonderling	Nil	Nil	Nil	Nil

** All staff members receive salary from the Royal College of Physicians and undertake commissions received from NICE.*

Appendix C: Review protocols

C.1 Review protocols for the 2014 guideline

C.1.1 Measuring kidney function

Table 1: Review protocol: measuring kidney function

Review question	**What is the accuracy of equations to estimate GFR as a measurement of kidney function?**
Objectives	To determine the most clinically and cost effective method of estimating GFR to assess kidney function.
Population:	Adults (aged 18 and over) with suspected CKD **Subgroups:** • Older people aged over 75 years • Black and minority ethnic groups
Index tests	• CKD-EPI GFR (serum creatinine) • Cystatin C estimating equations (cystatin C) • Combined CKD-EPI (serum creatinine + cystatin C) **Comparator test:** MDRD **Reference standard:** Measured GFR (urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]).
Outcomes	**Critical:** • Accuracy (P30) • Bias • Precision **Important:** • Sensitivity • Specificity ● Area under the receiver operating characteristic curve (AUC)Net reclassification index (NRI)
Study design	Diagnostic studies
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards
Review strategy	• Minimum n=100.

	• Limit to studies using international standardisation for serum creatinine and cystatin C. • Externally validated equations only. • Geographical exclusion – studies not relevant to population of England and Wales excluded as equations known to function differently in different populations. • Medians to be calculated for analysis of outcomes. Due to differences in gold standard mGFRs only studies with more than one equation that meets inclusion criteria will be considered.

C.1.2 Markers of kidney damage

Table 2: Review protocol: Markers of kidney damage

Review question	What is the best combination of measures of kidney function and markers of kidney damage to identify people with CKD who are at increased risk of progression?
Objectives	To determine the most clinically and cost effective combination of measures and markers to identify people with CKD who are at increased risk of progression.
Population	Adults (aged 18 and over) with CKD Subgroups Older people aged over 75 years Black and minority ethnic groups
Prognostic factor	MDRD (serum creatinine) plus urinary ACR CKD-EPI eGFR (serum creatinine) plus urinary ACR CKD-EPI cystatin C plus urinary ACR Combined CKD-EPI (serum creatinine + cystatin C eGFR) plus urinary ACR
Outcomes	• CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • AKI • All-cause mortality • Cardiovascular mortality
Covariates	Age, gender, hypertension and diabetes.
Study design	Prospective cohort studies (or retrospective cohorts if no prospective available)
Exclusions	Abstracts (excluded from review, not from search) Studies with N<100
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards
The review strategy	Minimum length of follow up: 1 year Minimum n=100 GFR category will be considered if reported (suggested sub-divisions <15, 15-29, 30-44, 45-59, 60-89, >90 ml/minml/min/1.73 m^2)

C.1.3 Classification of CKD

Table 3: Review protocol: Classification of CKD

Review question	**For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes (CKD progression, AKI, all-cause mortality and cardiovascular mortality)?**
Objectives	To determine whether occurrence of adverse outcomes is different in people with different levels of proteinuria compared to those without at any given eGFR.
Population	Adults (aged 18 and over) with suspected CKD **Subgroups:** • Older people (≥75 years) • People with hypertension (BP > 140/90 mmHg) • People with diabetes
Presence of prognostic factor	Proteinuria: ACR <3 mg/mmol (<30mg/g) ACR 3-29 mg/mmol (30-299mg/g) ACR >30 mg/mmol (>300mg/g) (or equivalent PCR and reagent strip result)
Absence of prognostic factor	Normal - increased proteinuria (ACR <3 mg/mmol)
Outcome	**Critical** • CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)All-cause mortality • Cardiovascular mortality • AKI **Important** • Cardiovascular events • Hospitalisation
Study design	Prospective cohort studies (Retrospective cohorts if no prospective identified)
Exclusions	Non English language studies Abstracts only (not excluded from the search)
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.4 Cause of CKD – Risk factors for adverse outcomes

C.1.4.1 Diabetes

Table 4: Review protocol: presence of diabetes on adverse outcomes

Review question	For people with CKD, does the presence of diabetes have an effect on adverse outcomes at any given category of eGFR and ACR?
Objectives	To determine whether occurrence of adverse outcomes is different in those with CKD associated with diabetes to those with CKD from another cause, at any given eGFR
Population	Adults aged over 18 with CKD
Presence of prognostic factor	Diabetes and CKD
Absence of prognostic factor	CKD and no known diabetes
Outcomes	**Adverse outcomes:** **Critical** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important** • Hospitalisation
Study design	Prospective cohort studies (or retrospective if no prospective studies identified) Cross sectional studies
Exclusions	Non English language studies. Abstracts (excluded from review, not from search)
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards
The review strategy	Will report type I & type II diabetes (or insulin / non-insulin dependent) separately if data available **Key papers:** Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis, The Lancet, Early Online Publication, 24 September 2012

C.1.4.2 Hypertension

Table 5: Review protocol: presence of hypertension on adverse outcomes

Review question	For people with CKD, does the presence of hypertension have an effect on adverse outcomes at any given category of eGFR and ACR?
Objectives	To determine whether occurrence of adverse outcomes is different in those with CKD associated hypertension
Population	Adults (aged 18 and over) with CKD
Presence of prognostic factor	Diagnosed hypertension and CKD (BP >140/90mmHg)
Absence of prognostic factor	CKD and no known hypertension
Outcomes	**Adverse outcomes:** **Critical** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important** Hospitalisation
Study design	Prospective cohort studies (or retrospective if no prospective studies identified) Cross sectional studies
Exclusions	Non English language studies. Abstracts (excluded from review, not from search)
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards
The review strategy	**Key papers:** Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis, The Lancet, Early Online Publication, 24 September 2012

C.1.4.3 Glomerular disease

Table 6: Review protocol: presence of glomerular disease on adverse outcomes

Review question	For people with CKD, does the presence of glomerular disease have an effect on adverse outcomes at any given category of eGFR and ACR?
Objectives	To determine whether occurrence of adverse outcomes is different in those with CKD

Review question	For people with CKD, does the presence of glomerular disease have an effect on adverse outcomes at any given category of eGFR and ACR?
	caused by glomerular disease
Population	Adults (aged 18 and over) with CKD
Presence of prognostic factor	CKD and glomerular disease
Absence of prognostic factor	CKD and no underlying glomerular disease
Outcomes	**Adverse outcomes:** **Critical** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important** Hospitalisation
Study design	Prospective cohort studies (or retrospective if no prospective studies identified) Cross sectional studies
Exclusions	Non English language studies. Abstracts (excluded from review, not from search)
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2002 onwards
The review strategy	Glomerular disease to include: proliferative glomerulonephritis, membranous glomerulonephritis, minimal-change nephropathy, IgA nephropathy, Focal glomerulosclerosis, nephrotic syndrome, focal segmental.

C.1.4.4 Acute kidney injury

Table 7: Review protocol: presence of acute kidney injury on adverse outcomes

Review question	For people with CKD, does the presence of acute kidney injury (AKI) have an effect on adverse outcomes at any given category of eGFR and ACR?
Objectives	To determine whether occurrence of adverse outcomes is different in those with CKD caused by acute kidney injury.
Population	Adults (aged 18 and over) with CKD
Presence of prognostic factor	CKD and acute kidney injury
Absence of	CKD and no known acute kidney injury (or history of)

Review question	For people with CKD, does the presence of acute kidney injury (AKI) have an effect on adverse outcomes at any given category of eGFR and ACR?
prognostic factor	
Outcomes	**Adverse outcomes:** **Critical** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important** • Hospitalisation
Study design	Prospective cohort studies (or retrospective if no prospective studies identified) Cross sectional studies
Exclusions	Non English language studies. Abstracts (excluded from review, not from search)
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2002 onwards

C.1.5 Frequency of monitoring

Table 8: Review protocol: frequency of monitoring

Review question	How frequently should eGFR, ACR or PCR be monitored in people with CKD?
Objectives	To determine how frequently eGFR, ACR or PCR should be measured for people diagnosed with CKD.
Population	Adults (aged 18 and over) with CKD
Prognostic factor	eGFR measure ACR measure PCR measure
Outcomes	CKD progression:change in eGFR CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) All-cause mortality Cardiovascular mortality
Study design	Prospective cohort studies (or retrospective if no prospective available) Cross sectional studies
Exclusions	Non English language studies. Abstracts (excluded from review, not from search)

Review question	How frequently should eGFR, ACR or PCR be monitored in people with CKD?
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards
The review strategy	Retrospective cohort studies will be considered if better quality studies not available Stage of CKD will be considered if reported e.g. eGFR >90 ml/min/1.73 m^2 eGFR 60-89 ml/min/1.73 m^2 eGFR 45-59 ml/min/1.73 m^2 eGFR 30-44 ml/min/1.73 m^2 eGFR 15-29 ml/min/1.73 m^2 eGFR<15 ml/min/1.73 m^2 . Threshold of 25% change in eGFR and cut-offs of 3 and 30mg/mmol for albuminuria to be used to mark significant change at various time points. Multivariate analysis with Hazard ratios will be considered the best quality outcome. Other analyses will only be considered if these are not available.

C.1.6 Progression of CKD after acute kidney injury

Table 9: Review protocol: progression to CKD after acute kidney injury

Review question	What is the risk of developing and/or progression of CKD after an episode of AKI?
Objectives	To determine whether the risk of developing CKD is different in those who have had acute kidney injury to those who haven't.
Population	Adults (aged 18 and over) **Subgroups:** • People aged over 75 years
Presence of prognostic factor	Prior episode of acute kidney injury
Absence of prognostic factor	No history of acute kidney injury
Outcomes	• Incident CKD; • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)
Study design	Prospective cohort studies; Cross sectional studies
Search	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2002 onwards
Review strategy	Severity of AKI will be considered if reported. GFR category at baseline will be considered if reported.

	Retrospective cohorts will be considered if no prospective cohorts identified.

C.1.7 Low protein diet

Table 10: Review protocol: low protein diet

Review question	For people with CKD, are low protein diets a clinically and cost effective method for the management of CKD?
Guideline condition and its definition	Adults with chronic kidney disease. Definition:
Review population	Adults (aged 18 and over) with CKD
	Adults aged 18 and over
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Low protein diet; Low protein diet (0.6 - 0.8g/kg) Higher protein diet; Higher protein diet (greater than 0.8g/kg) Higher protein diet; Higher protein diet (unrestricted or free protein)
Outcomes	• Quality of life (Critical) at 1 year minimum (Continuous) • Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum (Time to event; MID: Other) • Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum (Continuous) • Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum (Time to event; MID: Other) • Compliance (measured by actual protein intake) (Important) at 1 year minimum (Continuous) • Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum (Dichotomous) • Nutritional status (measured by change in BMI) (Important) at 1 year minimum (Continuous)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	1 year
Allocation concealment	Adequate and unclear
Other exclusions	Renal replacement therapy
Sensitivity/other analysis	• Continous outcomes - final values preferred. Change scores and final values will be pooled if required. • Time to event outcomes will be reported as dichotomous if time to event data not available.

	• Stage of CKD at time of administration will be considered if reported. • Different levels of protein restriction will be considered if reported. • Progression of CKD measured by creatinine clearance will be considered if GFR not reported
Subgroup analyses if there is heterogeneity	• Older people aged 75 years and over (Aged 75 or over; Aged under 75; RCT: mixed); People aged 75 years and over may have greater risks associated with a low protein diet. • People with diabetes (CKD and diabetes; CKD only); People with diabetes may have greater difficulty adhering to a diet which is low protein and also suitable for diabetes.
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.8 Self-management

Table 11: Review protocol: Self-management support systems

Review question	**For people with CKD, what is the clinical and cost effectiveness of self-management support systems?**
Guideline condition and its definition	Adults with chronic kidney disease.
Review population	Adults aged 18 or over with chronic kidney disease
	Adults aged 18 or over
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Usual care Self management support system
Outcomes	• Health related quality of life (Important) at At stated in paper (Continuous) • Mortality (all-cause and cardiovascular) (Critical) at At stated in paper (Time to event; MID: Other) • Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at At stated in paper (Time to event; MID: Other) • Progression of CKD (change in eGFR) (Important) at At stated in paper (Continuous) • Hospitalisation (Important) at At stated in paper (Time to event; MID: Other) • Adherence to treatment at At stated in paper (Dichotomous) • Outpatient attendance at At stated in paper (Dichotomous)

Review question	For people with CKD, what is the clinical and cost effectiveness of self-management support systems?
Study design	Systematic Review RCT Non randomised study
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Allocation concealment	Adequate and unclear
Other exclusions	Dialysis patients
Sensitivity/other analysis	Continuous outcomes - final values preferred. Change scores and final values will be pooled if required Time to event outcomes - will be reported as dichotomous if time to event data not available Stage of CKD at time of administration will be considered if reported Doses will be pooled for analysis. Time points will be pooled for analysis (<1 year, 1year – 18 months, 18 months – 3 years etc.)
Subgroup analyses if there is heterogeneity	- Older people aged 75 or over (Aged 75 or over; Aged under 75; Mixed); People over 75 are at greater risk of renal bone disease - People with diabetes (People with diabetes; People without diabetes); People with diabetes are likely to respond differently to treatment - People from BME gps (People from BME gps; People not from BME gps); Peoplefrom BME gps may respond differently to treatment
Search criteria	Databases: Date limits for search: Language: Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.9 Blood pressure - combined renin-angiotensin-aldosterone system antagonists

Table 12: Review protocol: Renin-angiotensin-aldosterone system antagonists

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
Guideline condition and its definition	Adults with chronic kidney disease.
Review population	Adults aged 18 or over with chronic kidney disease
	Adults aged 18 or over

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Placebo ACE inhibitors; Captopril ACE inhibitors; Cilazapril ACE inhibitors; Enalapril ACE inhibitors; Fosinopril ACE inhibitors; Imidapril ACE inhibitors; Lisinopril ACE inhibitors; Perindopril ACE inhibitors; Ramipril ACE inhibitors; Trandolapril Angiotensin-II receptor blockers; Azilsartan Angiotensin-II receptor blockers; Candesartan Angiotensin-II receptor blockers; Eprosartan Angiotensin-II receptor blockers; Irbesartan Angiotensin-II receptor blockers; Losartan Angiotensin-II receptor blockers; Olmesartan Angiotensin-II receptor blockers; Telmisartan Angiotensin-II receptor blockers; Valsartan Aldosterone antagonists; Spironolactone Aldosterone antagonists; Eplerenone Direct renin inhibitors; Aliskiren ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Captopril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Cilazapril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Enalapril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Azilsartan

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
	ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Fosinopril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Imidapril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Imidapril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Imidapril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Imadapril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Imadapril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Imadapril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Imadapil and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Imadapril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Candesartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Losartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Olmesartan

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
	ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; Trandolapril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Perindopril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Ramipril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; Lisinopril and Valsartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Azilsartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Candersartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Eprosartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Irbesartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Losartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Olmesartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Telmisartan ACE inhibitors and Angiotensin-II receptor blockers; ACEI (mixed) and Valsartan Aldosterone antagonist and ACE inhibitor; Spironolactone and ACE inhibitor Aldosterone antagonist and ACE inhibitor; Eplerenone and ACE inhibitor Aldosterone antagonist and ARB; Spironolactone and ARB Aldosterone antagonist and ARB; Eplerenone and ARB Aldosterone antagonist and ACE inhibitor and ARB; Spironolactone and ACEI and ARB Aldosterone antagonist and ACE inhibitor and ARB; Eplerenone and ACEI and ARB Direct renin inhibitor and ACE inhibitor; Aliskiren and ACEI Direct renin inhibitor and ARB; Aliskiren and ARB Direct renin inhibitor and ACE inhibitor and ARB; Aliskiren and ACEI and ARB Placebo and standard therapy; Placebo and ACEI Placebo and standard therapy; Placebo and ARB Placebo and standard therapy; Placebo and ACEI and ARB
Outcomes	• Health related quality of life (Important) at 12 months minimum (Continuous) • Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum (Time to event; MID: Other) • Cardiovascular events (Critical) at 12 months minimum (Time to event; MID: Other) • Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum (Time to event; MID: Other) • Progression of CKD (change in eGFR) (Critical) at 12 months minimum (Continuous) • Hospitalisation (Important) at 12 months minimum (Time to event; MID: Other) • Acute kidney injury (Critical) at 12 months minimum (Dichotomous) • Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
	months minimum (Continuous)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	12 months
Allocation concealment	Adequate and unclear
Other exclusions	Dialysis patients
Population stratification	CKD without diabetes CKD with diabetes
Reasons for stratification	Clinicians would manage an ACR between 3-30 mg/mmol differently in people with diabetes compared to those without - so different recommedations may be required for these populations.
Sensitivity/other analysis	Continuous outcomes - final values preferred. Change scores and final values will be pooled if required Time to event outcomes - will be reported as dichotomous if time to event data not available Stage of CKD at time of administration will be considered if reported Doses will be pooled for analysis. Time points will be pooled for analysis (<1 year, 1year – 18 months, 18 months – 3 years etc.) Mixed treatment comparisons by meta-analysis will be considered Measures of proteinuria will be combined using a table of equivalence
Subgroup analyses if there is heterogeneity	- Older people aged 75 or over (Aged 75 or over; Aged under 75; Mixed); People over 75 are at greater risk of cardiovascular disease and renal progression - People with proteinuria (ACR <3mg/mmol; ACR 3-30 mg/mmol; ACR >30 mg/mmol); People with proteinuria are at increased risk of renal progression - People with diabetes and proteinuria (People with diabetes and ACR <2.5mg/mmol; People with diabetes and ACR 2.5-3.0 mg/mmol; People with diabetes and ACR >3.0mg/mmol); People with diabetes and proteinuria at increased risk of progression at lower levels than general population - People with hypertension (Blood pressure <140/90mmHg; Blood pressure >140/90mmHg); People with hypertension are at greater risk of cardiovascular disease and renal progression - People with cardiovascular disease (People with cardiovascular disease; People without cardiovascular disease); People with cardiovascular disease are at greater risk of cardiovascular events and renal progression

Review question	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?
	- Black and minority ethnic groups (BME; Not BME); People from BME groups may be at greater risk of cardiovascular disease and renal progression
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.10 Oral antiplatelets and anticoagulants

Table 13: Review protocol: anticoagulants and oral antiplatelets

Review question	For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?
Guideline condition and its definition	Adults with chronic kidney disease. Definition:
Review population	Adults aged 18 or over with chronic kidney disease
	Adults aged 18 or over
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Placebo Antiplatelet agents; Aspirin Antiplatelet agents; Ticagrelor Antiplatelet agents; Clopidogrel Antiplatelet agents; Prasugrel Antiplatelet agents; Ticagrelor and aspirin Antiplatelet agents; Clopidogrel and aspirin Oral anticoagulants; Dabigatran Oral anticoagulants; Apixaban Oral anticoagulants; Rivaroxaban Oral anticoagulants; Warfarin
Outcomes	- Health related quality of life (Important) at 6 months minimum (Continuous) - Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum (Time to event; MID: Other) - Cardiovascular or cerebrovascular events (Critical) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (change in eGFR) (Important) at 6 months minimum (Continuous) - Hospitalisation (Important) at 6 months minimum (Time to event; MID: Other) - Major bleeding (as reported by studies) (Critical) at 6 months minimum (Time to event; MID: Other) - Minor bleeding (as reported by the studies) (Important) at Define (Dichotomous)

Review question	For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Allocation concealment	Adequate and unclear
Other exclusions	Dialysis patients
Sensitivity/other analysis	Continuous outcomes - final values preferred. Change scores and final values will be pooled if required Time to event outcomes - will be reported as dichotomous if time to event data not available Stage of CKD at time of administration will be considered if reported Doses will be pooled for analysis. Time points will be pooled for analysis (<1 year, 1year – 18 months, 18 months – 3 years etc.)
Subgroup analyses if there is heterogeneity	- Older people aged 75 or over (Aged 75 or over; Aged under 75; Mixed); People over 75 are at greater risk of renal bone disease - People with cardiovascular disease (People without cardiovascular disease; People with cardiovascular disease); People with atrial fibrillation are at greater risk of cardiovascular and cerebrovascular events
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.11 Asymptomatic hyperuricaemia

Table 14: Review protocol: Asymptomatic hyperuricaemia

Review question	For people with CKD and asymptomatic hyperuricaemia, what is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?
Guideline condition and its definition	Adults aged 18 or over. Definition:
Review population	Adults aged 18 and over with chronic kidney disease and asymptomaic hyperuricaemia
	Adults aged 18 and over
	Line of therapy not an inclusion criterion
Interventions and comparators:	Uric acid lowering therapies; Allopurinol Uric acid lowering therapies; Febuxostat

Review question	For people with CKD and asymptomatic hyperuricaemia, what is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?
generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	
Outcomes	- Quality of life at 3 months (Continuous) - Hospitalisation at 3 months (Time to event; MID: Other) - Cardiovascular events at 3 months (Dichotomous) - Reduction in antihypertensive agents at 3 months (Dichotomous) - Renal progression - eGFR (final values) at 3 months (Dichotomous) - Renal progression - end stage renal disease needing RRT at 3 months (Dichotomous) - All-cause mortality at 3 months (Time to event; MID: Other) - Serious adverse events at 3 months (Dichotomous) - Cardiovascular mortality at 3 months (Time to event; MID: Other)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other inclusions	--Define--
Subgroup analyses if there is heterogeneity	- Aged 75 or older or under 75 (Aged 75 or over; Aged under 75; Systematic review (mixed)); People aged over 75 may respond differently to the intervention
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

Table 15: Review protocol: Vitamin D supplementation for the management of renal bone disease?

Review question	For people with GFR 15-60 ml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?
Guideline condition and its definition	Adults with chronic kidney disease. Definition:
Review population	Adults aged 18 or over with chronic kidney disease and GFR 15-60

Review question	For people with GFR 15-60 ml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?
	Adults aged 18 or over
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Vitamin D; Ergocalciferol (Vitamin D2) Vitamin D; Alfacalcidol (1 alpha hydroxycholecalciferol) Vitamin D; Calcitriol (1,25 dihidroxycholecalciferol) Vitamin D; Cholecalciferol (Vitamin D3) Vitamin D; Dihydrotachysterol Vitamin D; Paracalcitrol Vitamin D; Doexercalciferol Placebo
Outcomes	- Health related quality of life (Important) at 6 months minimum (Continuous) - Mortality (all cause) (Critical) at 6 months minimum (Time to event; MID: Other) - Cardiovascular events (Critical) at 6 months minimum (Time to event; MID: Other) - Fracture (Critical) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (change in eGFR) (Critical) at 6 months minimum (Continuous) - Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum (Dichotomous) - Hospitalisation (Important) at 6 months minimum (Time to event; MID: Other) - Mortality (cardiovascular) (Critical) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (creatinine clearance) at Define (Continuous)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Other inclusions	GFR 15-60ml/minml/min/1.73 m2
Allocation concealment	Adequate and unclear
Other exclusions	Dialysis patients
Sensitivity/other analysis	Continuous outcomes - final values preferred. Change scores and final values will be pooled if required Time to event outcomes - will be reported as dichotomous if time to event data not available Stage of CKD at time of administration will be considered if reported
Subgroup analyses if there is heterogeneity	- Older people aged 75 or over (Aged 75 or over; Aged under 75; Mixed); People over 75 are at greater risk of renal bone disease - Black and minority ethnic groups (RCT mixed population; BME; Not BME);

Review question	**For people with GFR 15-60 ml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?**
	BME groups are at increased risk - People with secondary hyperparathyroidism (CKD and secondary hyperparathyroidism; CKD only; Secondary hyperparathyroidism (cause not stated)); People with secondary hyperparathyroidism as well as CKD may respond differently
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only Search from 2007 onwards

C.1.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

Table 16: Review protocol: Oral bicarbonate supplements for the management of CKD

Review question	**What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?**
Guideline condition and its definition	Adults with chronic kidney disease. Definition:
Review population	Adults aged 18 or over with chronic kidney disease
	Adults aged 18 or over
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug **(All interventions will be compared with each other, unless otherwise stated)**	Placebo Oral bicarbonate supplements; Sodium bicarbonate Usual care
Outcomes	- Health related quality of life (Important) at 6 months minimum (Continuous) - Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum (Time to event; MID: Other) - Cardiovascular events (including chronic heart failure) (Critical) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 6 months minimum (Time to event; MID: Other) - Progression of CKD (change in eGFR) (Critical) at 6 months minimum (Continuous) - Hypertension (measured by use of antihypertensives) (Critical) at 6 months minimum (Dichotomous) - Hospitalisation (Important) at 6 months minimum (Time to event; MID: Other)

Review question	What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?
	- Alkalosis (Critical) at 6 months minimum (Dichotomous) - Nutrition (measured by subjective global assessment) (Critical) at 6 months minimum (Continuous) - Nutrition (measured by change in BMI) (Critical) at 6 months minimum (Continuous)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Allocation concealment	Adequate and unclear
Other exclusions	Dialysis patients
Sensitivity/other analysis	Continuous outcomes - final values preferred. Change scores and final values will be pooled if required Time to event outcomes - will be reported as dichotomous if time to event data not available Stage of CKD at time of administration will be considered if reported Usual care will be considered as a comparator if no placebo controlled RCTs are identified. Doses will be pooled for analysis. Time points will be pooled for analysis (<1 year, 1year – 18 months, 18 months – 2 years etc.)
Subgroup analyses if there is heterogeneity	- Older people aged 75 or over (Aged 75 or over; Aged under 75; Mixed); People over 75 are at greater risk of renal bone disease
Search criteria	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only No date restrictions

C.2 Economic review protocol for the 2014 guideline

Table 17: Economic review protocol for the 2014 guideline

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix F.

Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. **Inclusion/exclusion criteria** • If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations(a) • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) • Non-OECD settings (always 'Not applicable') *Economic study type:* • Cost-utility analysis • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) • Comparative cost analysis • Non-comparative cost analyses including cost of illness studies (always 'Not applicable') *Year of analysis:* • The more recent the study, the more applicable it is *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision

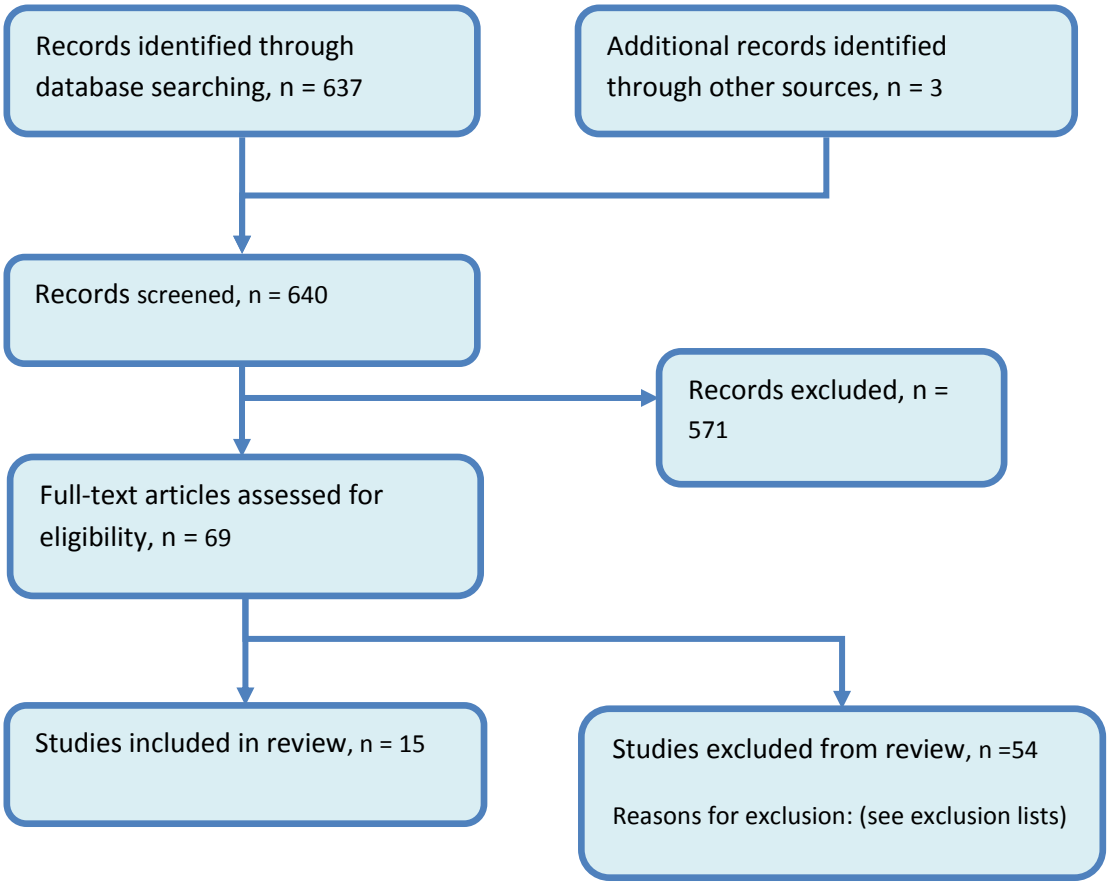
	making for the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Clinical article selection (2014)

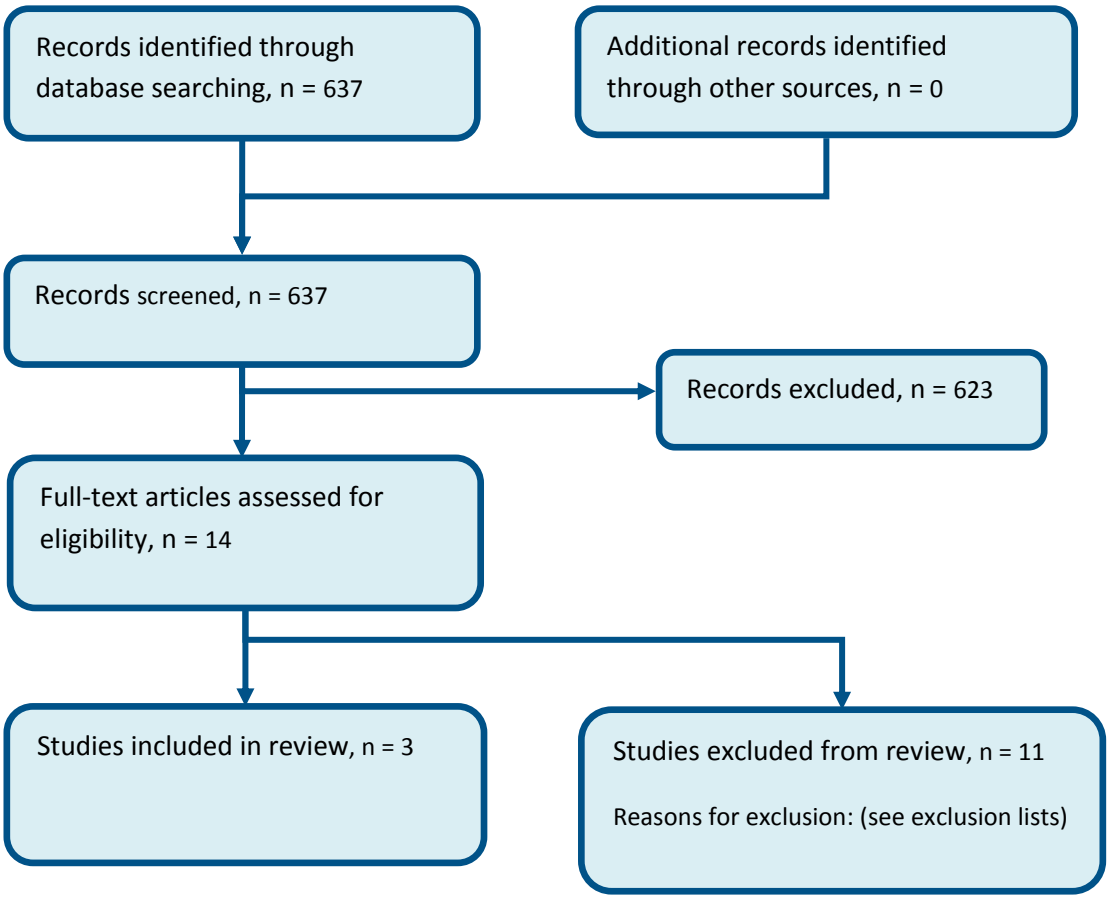
D.1 Measuring kidney function

Figure 1: Flow diagram of article selection for measurement of kidney function review



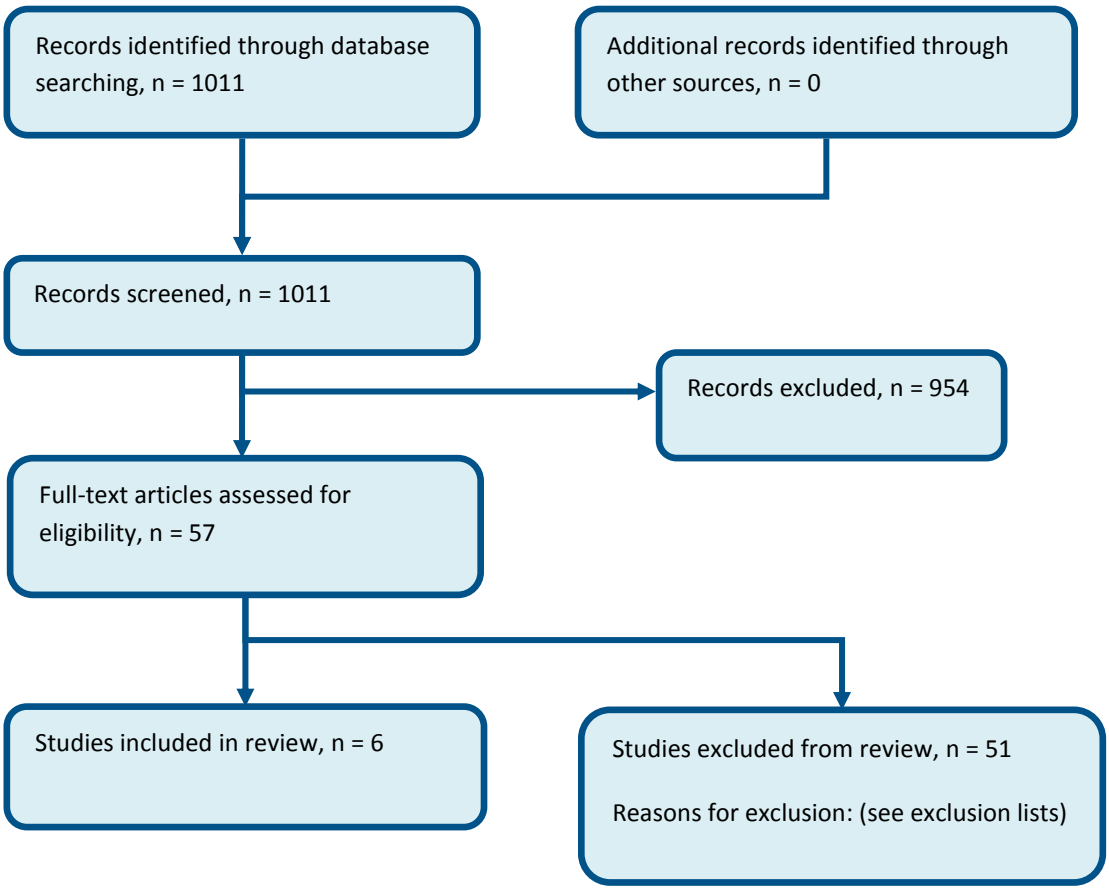
D.2 Markers of kidney damage

Figure 2: Flow diagram of article selection for markers of kidney damage review



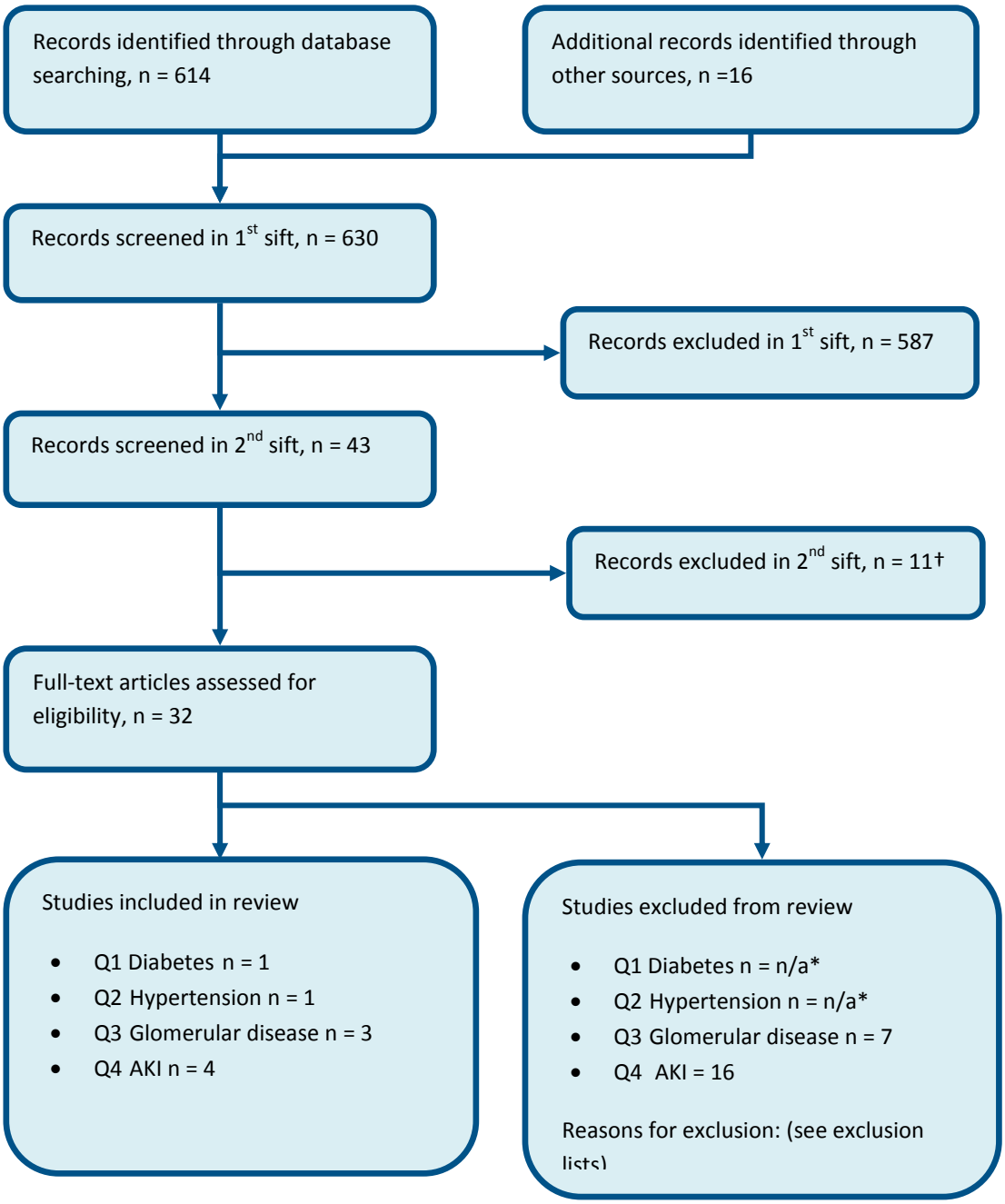
D.3 Classification of CKD

Figure 3: Flow diagram of article selection for classification of CKD review



D.4 Cause of CKD – risk factors for adverse outcomes

Figure 4: Flow diagram of clinical article selection for 'cause of CKD' review

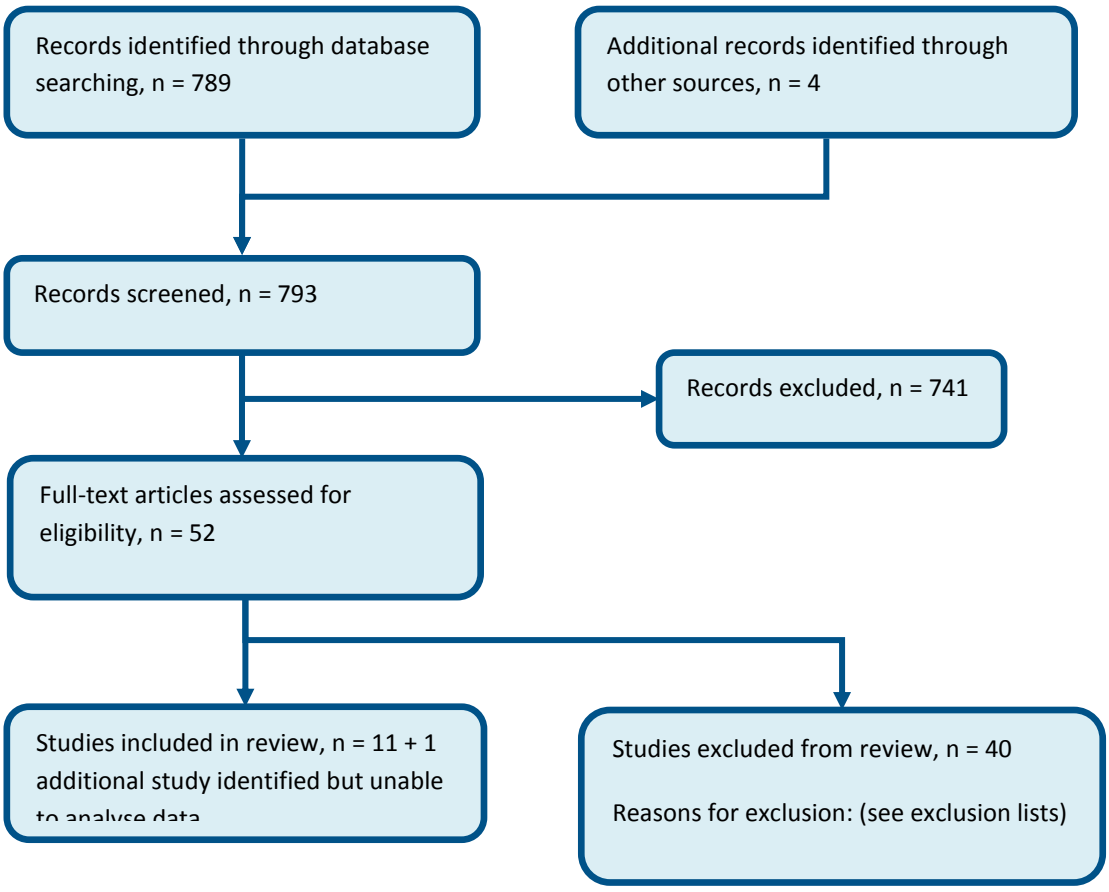


†AKI papers to be considered in 'risk of AKI review'

** IPD meta-analyses identified by previous review, directly relevant to this question, therefore new search not undertaken.*

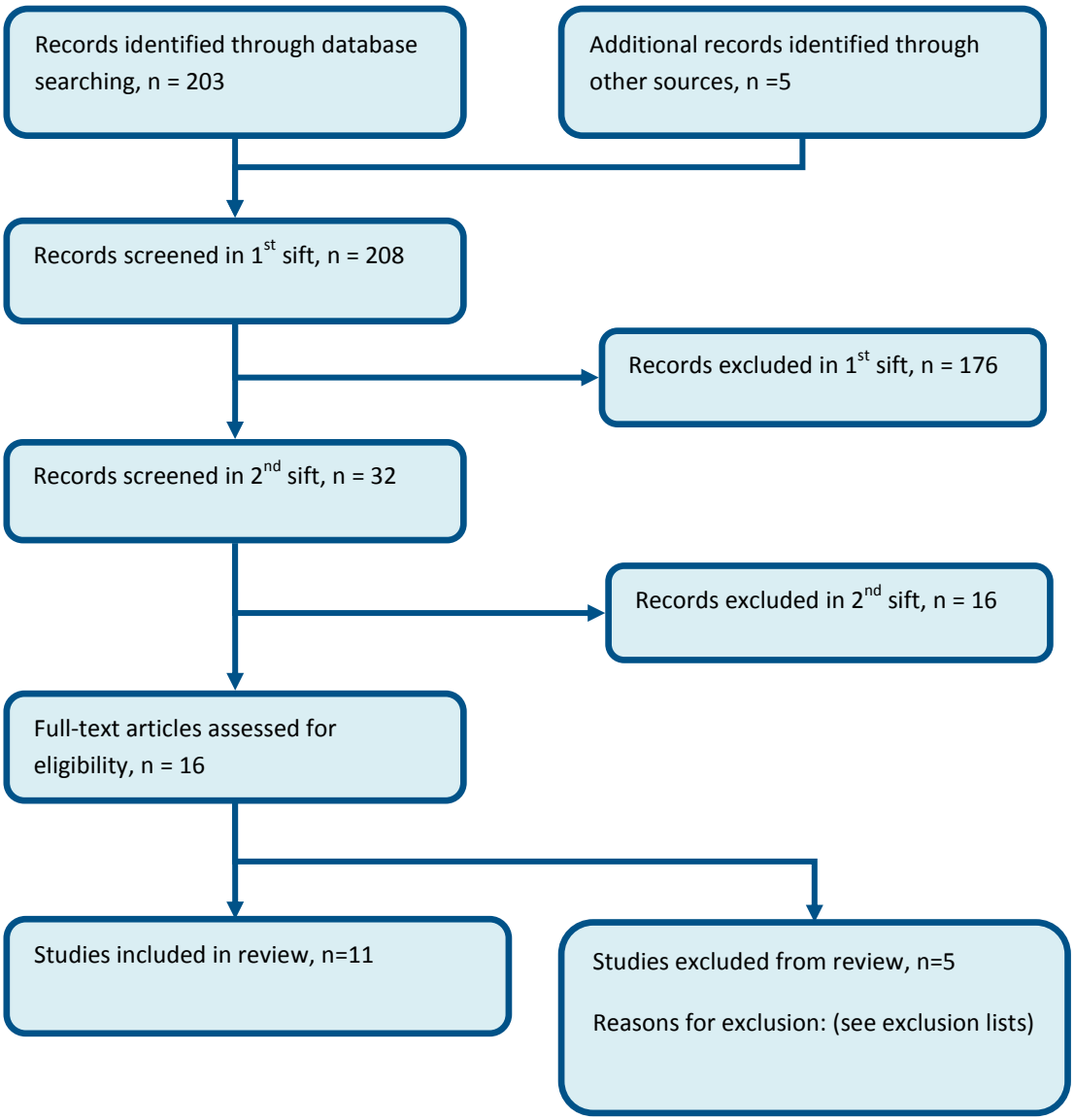
D.5 Frequency of monitoring

Figure 5: Flow diagram of article selection for frequency of monitoring review



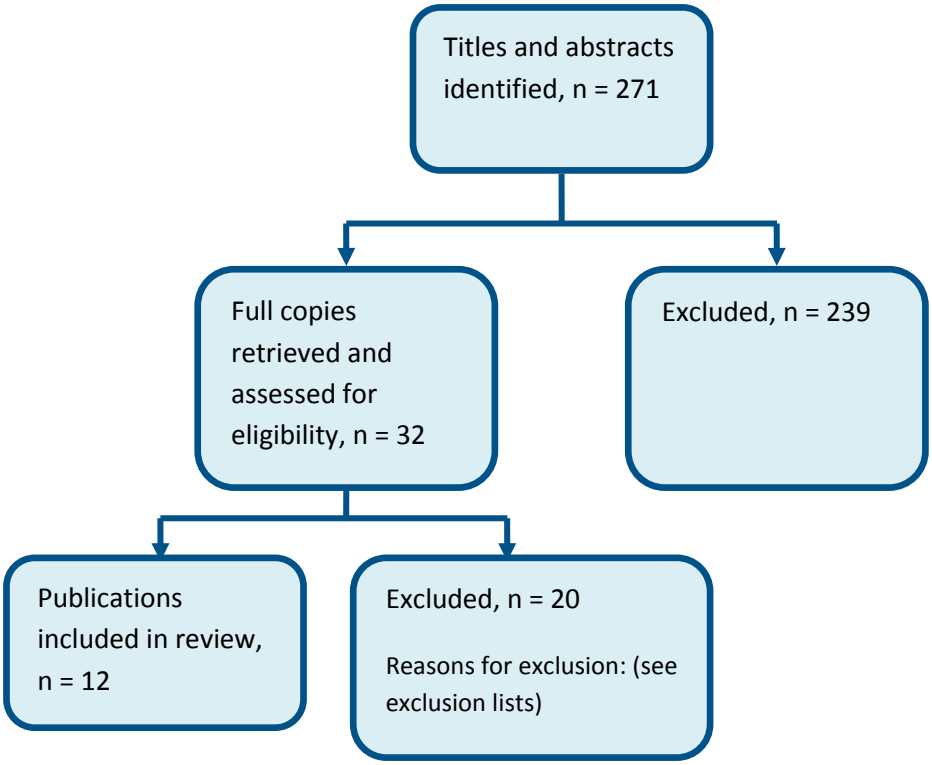
D.6 Progression of/to CKD after acute kidney injury

Figure 6: Flow diagram of clinical article selection for the review of progression after AKI



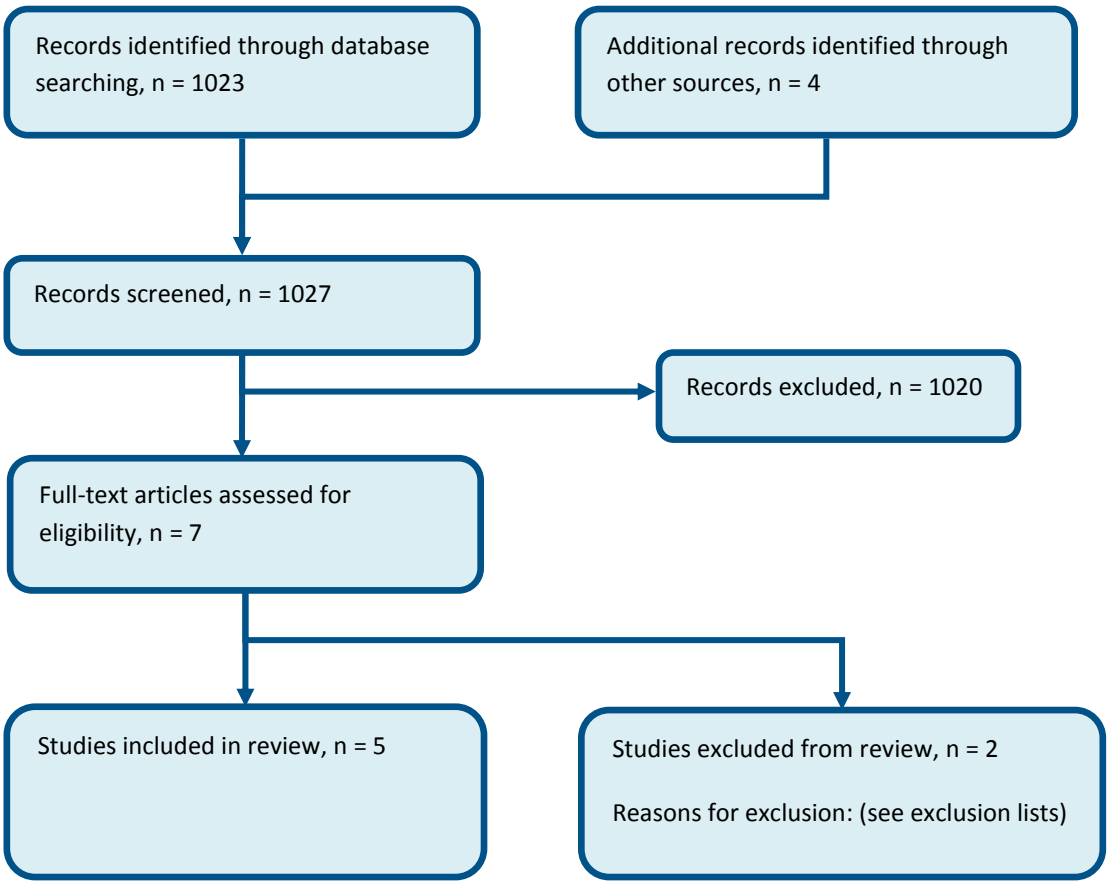
D.7 Low protein diet

Figure 7: Flow diagram of clinical article selection for low protein diet review



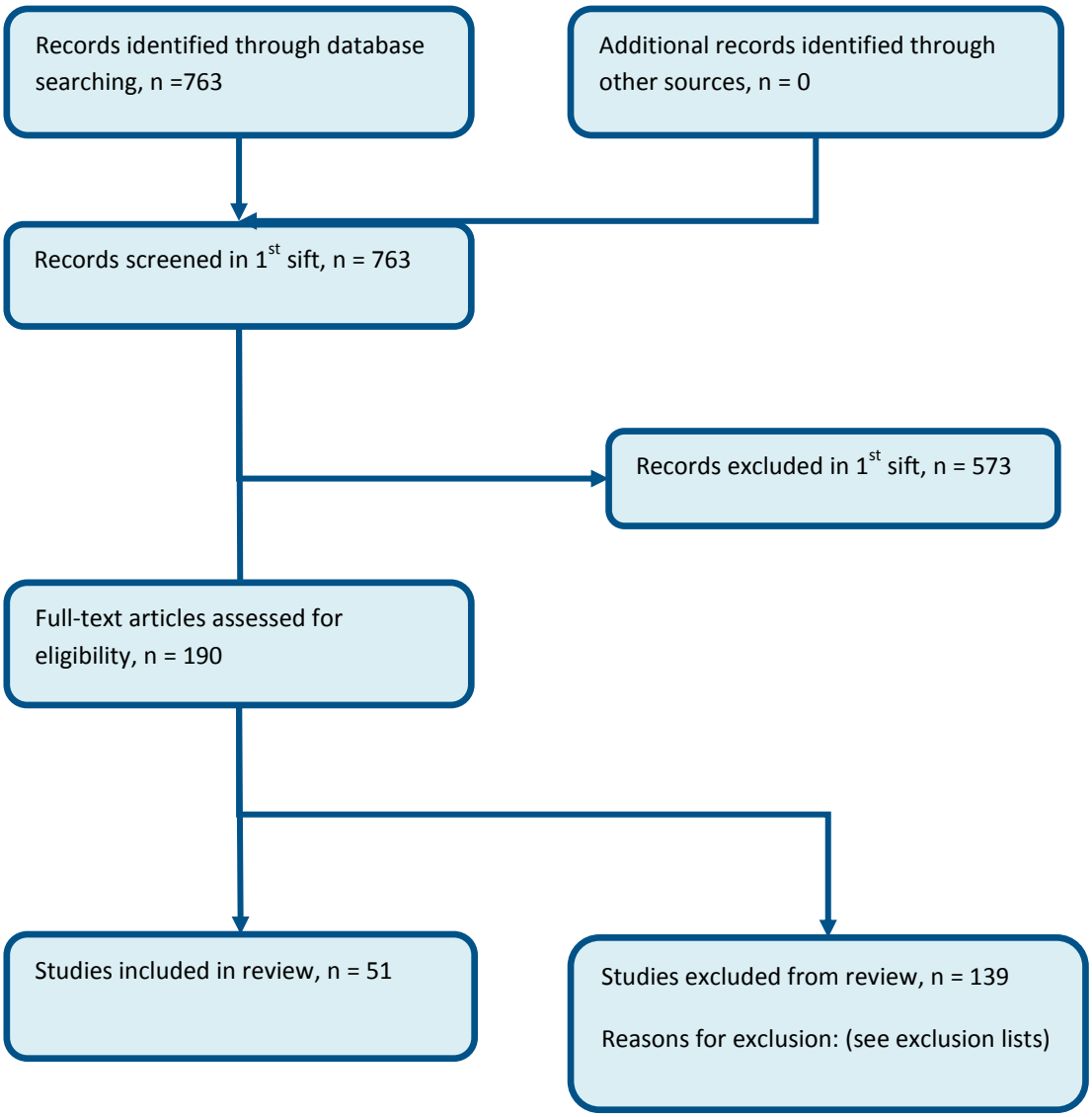
D.8 Self-management

Figure 8: Flow diagram of article selection for self-management support systems review



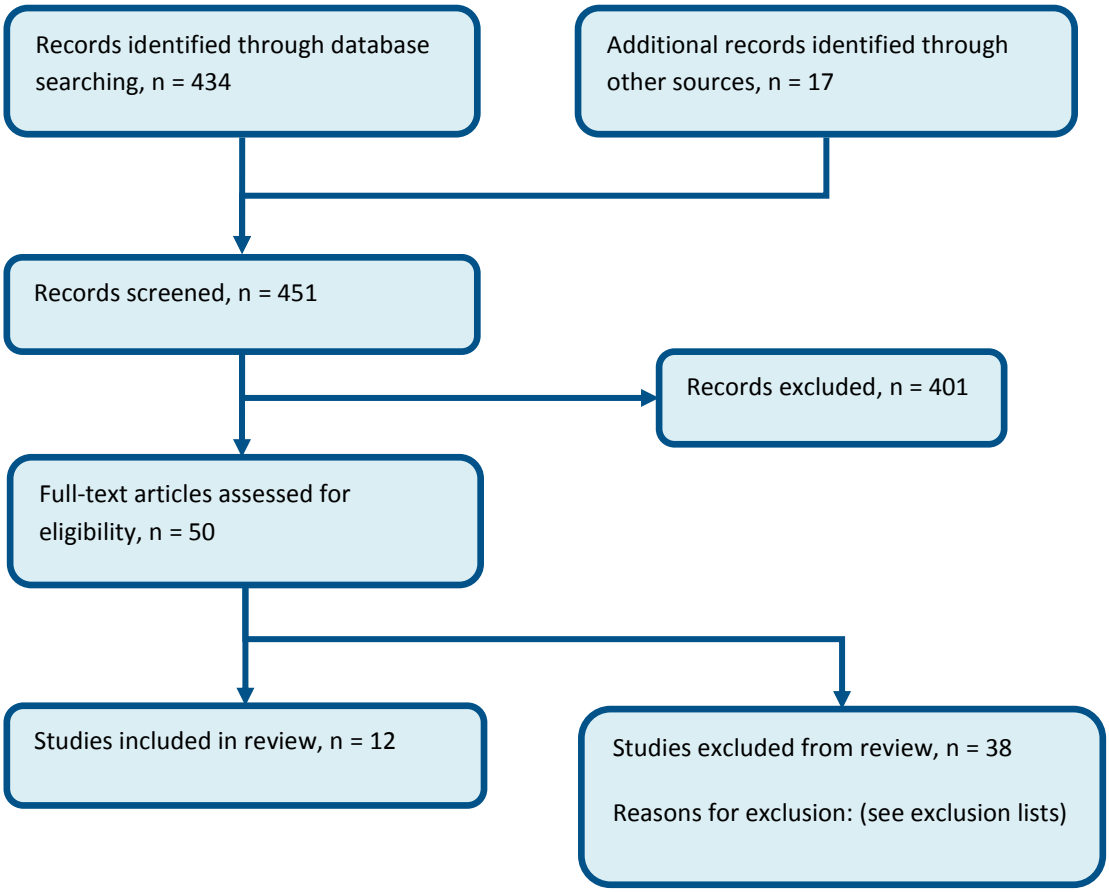
D.9 Blood pressure – combined renin-angiotensin-aldosterone system antagonists

Figure 9: Flow diagram of clinical article selection for RAAS antagonists review



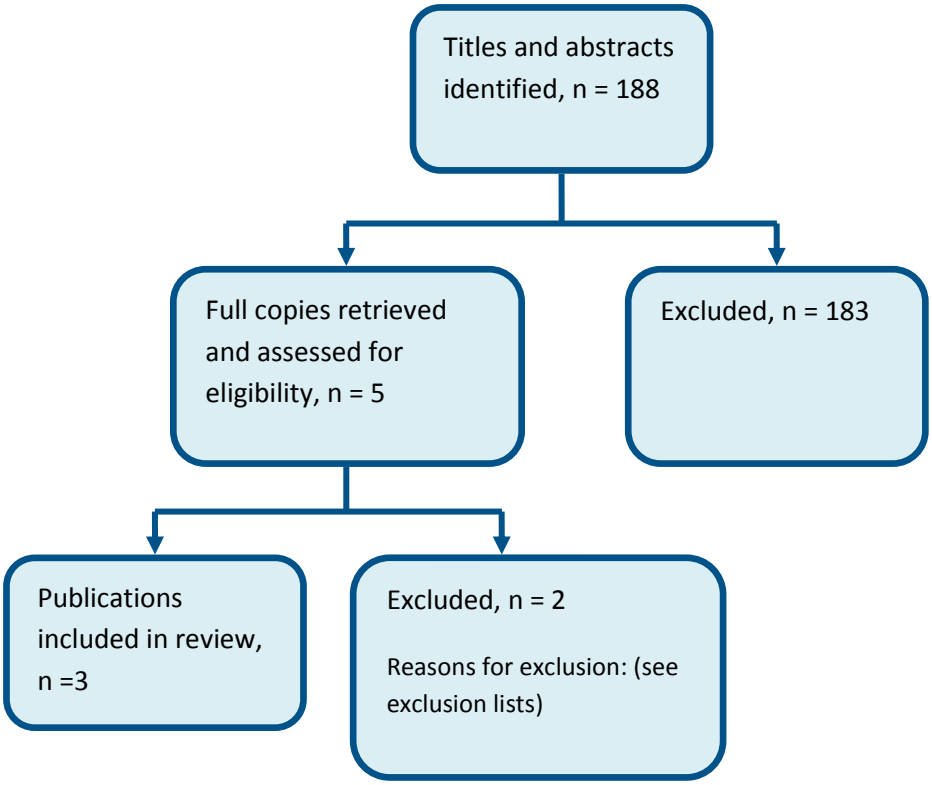
D.10 Oral antiplatelets and anticoagulants

Figure 10: Flow diagram of article selection for anticoagulants and antiplatelets review



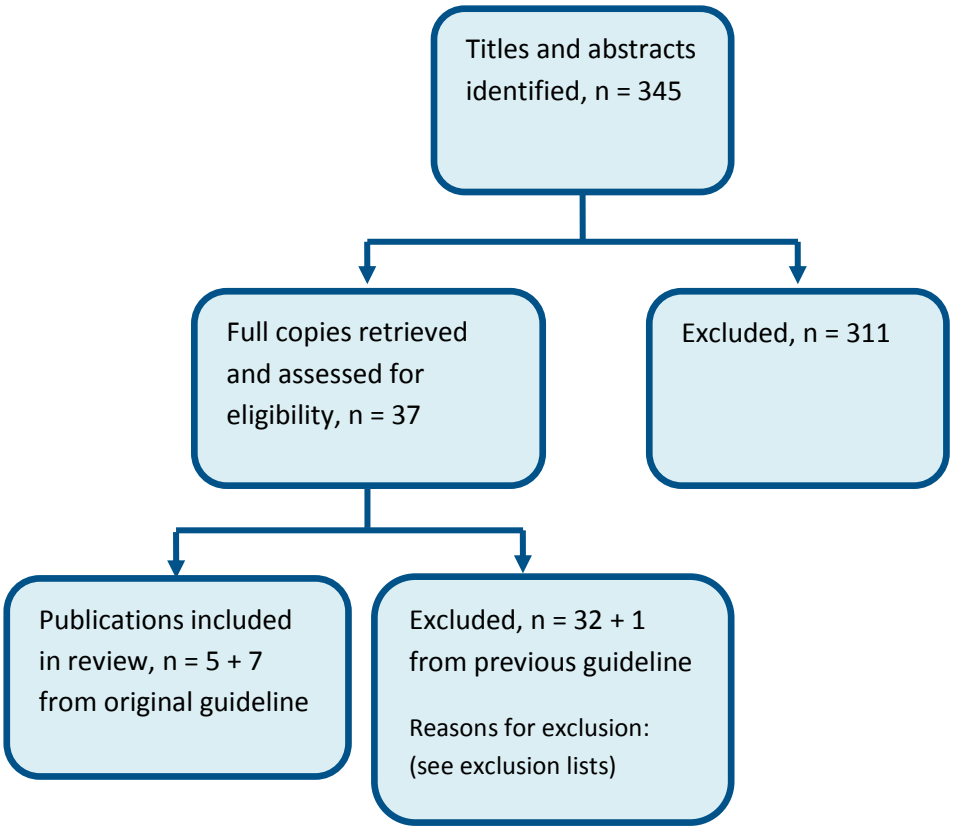
D.11 Asymptomatic hyperuricaemia

Figure 11: Flow diagram of clinical article selection for asymptomatic hyperuricaemia review



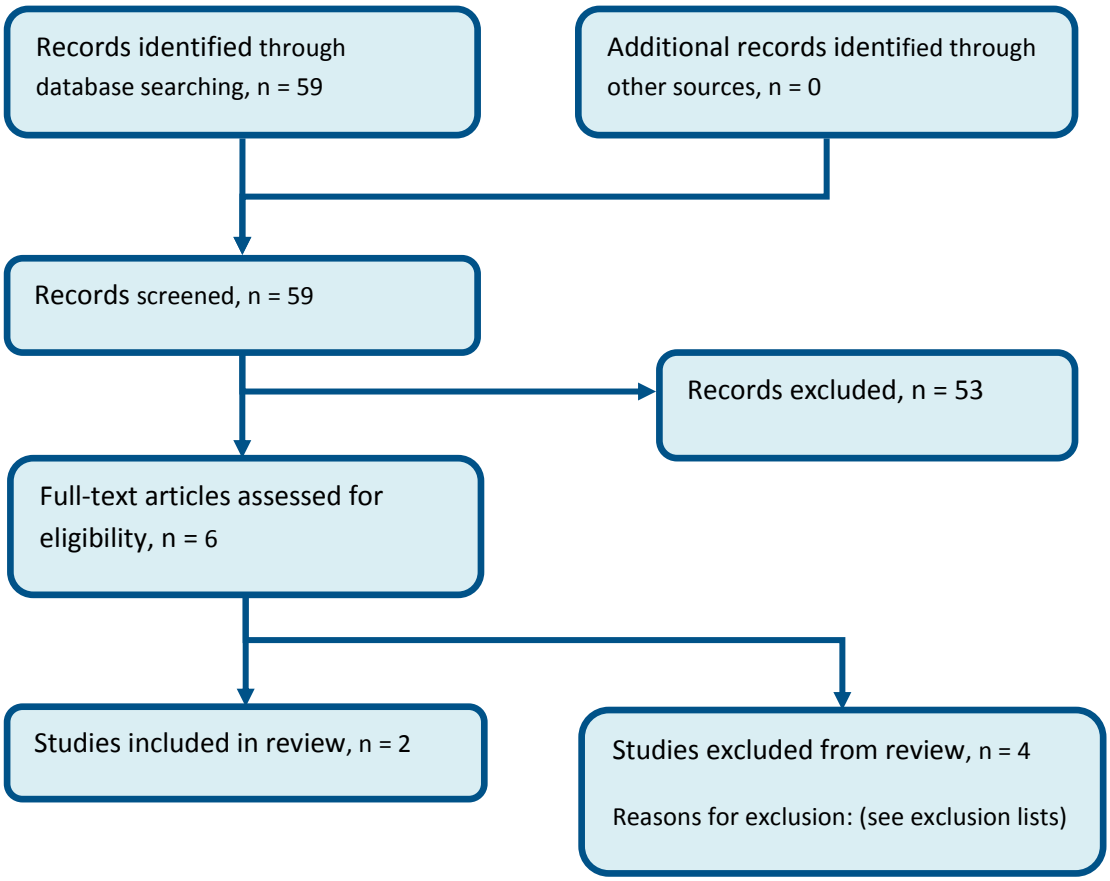
D.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

Figure 12: Flow diagram of clinical article selection for vitamin D supplements



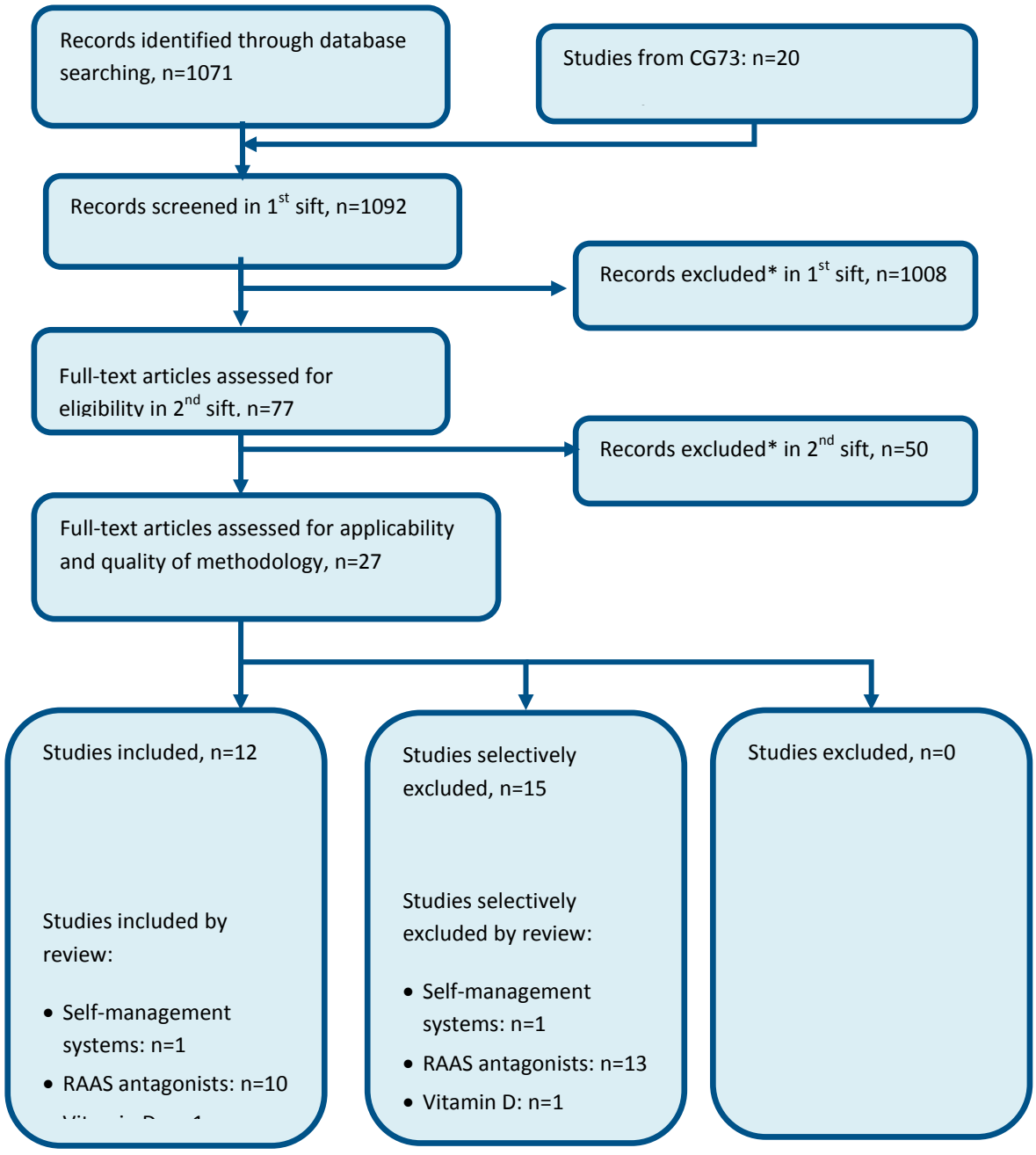
D.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

Figure 13: Flow diagram of article selection for oral bicarbonate supplements review



Appendix E: Economic article selection

Figure 14: Flow diagram of economic article selection for guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix F: Literature search strategies

Contents

Search strategies used for the chronic kidney disease guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2012.[481] All searches were run up to 25 November 2013 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with Intervention (I) and sometimes comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED via CRD), the Health Technology Assessment (HTA via CRD) database and the Health Economic Evaluation Database (HEED). Searches in CRD and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

F.1 Population search strategies

Medline search terms

1	renal insufficiency, chronic/
2	exp kidney failure, chronic/
3	kidney diseases/ and chronic.ti,ab.
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.
6	CKD.ti,ab.
7	diabetic nephropathies/
8	exp glomerulonephritis/
9	exp proteinuria/
10	acidosis, renal tubular/
11	exp hypertension, renal/
12	(diabetic adj (kidney or renal) adj (disease* or failure)).ti,ab.
13	((renal or renovascular) adj2 hypertensi*).ti,ab.
14	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.
15	(glomerular adj (sclerosis or nephritis)).ti,ab.
16	((renal or distal or proximal or tubul*) adj2 acidos*).ti,ab.
17	hyperuricemia/ or hyperuric?emi*.ti,ab.
18	exp hyperparathyroidism, secondary/
19	(renal adj2 (osteo* or hyperparathyroidism)).ti,ab.
20	or/1-19
21	ureteral obstruction/
22	exp urethral obstruction/
23	((uropath* or ureter* or urethra*) adj obstruct*).ti,ab.

24	(renal of kidney or chronic).ti,ab.
25	(21 or 22 or 23) and 24
26	20 or 25
27	(transplant* or donor* or graft* or allograft*).ti.
28	pregnan*.ti.
29	*renal dialysis/ not (predialysis or pre dialysis or ("not" adj4 dialysis)).ti.
30	26 not (27 or 28 or 29)

Embase search terms

1	chronic kidney disease/
2	chronic kidney failure/
3	(kidney failure/ or kidney disease/) and chronic.ti,ab.
4	((chronic or progressive) adj2 (renal or kidney)).ti,ab.
5	(chronic adj (kidney or renal) adj insufficienc*).ti,ab.
6	CKD.ti,ab.
7	diabetic nephropathy/
8	exp glomerulonephritis/
9	exp proteinuria/
10	kidney tubule acidosis/
11	renovascular hypertension/
12	(diabetic adj (kidney or renal) adj (disease* or failure)).ti,ab.
13	((renal or renovascular) adj2 hypertensi*).ti,ab.
14	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.
15	(glomerular adj (sclerosis or nephritis)).ti,ab.
16	((renal or distal or proximal or tubul*) adj2 acidos*).ti,ab.
17	hyperuricemia/ or hyperuric?emi*.ti,ab.
18	secondary hyperparathyroidism/ or renal osteodystrophy/
19	(renal adj2 (osteo* or hyperparathyroidism)).ti,ab.
20	or/1-19
21	obstructive uropathy/
22	exp urinary tract obstruction/
23	((uropath* or ureter* or urethra*) adj obstruct*).ti,ab.
24	(renal or chronic or kidney).ti,ab.
25	(21 or 26 or 23) and 24
26	20 or 25
27	(transplant* or donor* or graft* or allograft*).ti.
28	pregnan*.ti.
29	*hemodialysis/ not (predialysis or pre dialysis or ("not" adj4 dialysis)).ti.
30	26 not (27 or 28 or 29)

Cochrane search terms

#1	MeSH descriptor Renal Insufficiency, Chronic, this term only
#2	MeSH descriptor Kidney Failure, Chronic explode all trees
#3	MeSH descriptor Kidney Diseases explode all trees
#4	chronic:ti,ab
#5	(#1 OR #2 OR (#3 AND #4))
#6	((chronic or progressive) NEAR/2 (renal or kidney)):ti,ab
#7	(chronic NEXT (kidney or renal) NEXT insufficienc*):ti,ab
#8	CKD:ti,ab
#9	MeSH descriptor Diabetic Nephropathies, this term only
#10	MeSH descriptor Glomerulonephritis explode all trees
#11	MeSH descriptor Proteinuria explode all trees
#12	MeSH descriptor Acidosis, Renal Tubular, this term only
#13	MeSH descriptor Hypertension, Renal explode all trees
#14	(diabetic NEXT (kidney or renal) NEXT (disease* or failure)):ti,ab
#15	((renal or renovascular) NEAR/2 hypertensi*):ti,ab
#16	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria):ti,ab
#17	(glomerular NEXT (sclerosis or nephritis)):ti,ab
#18	((renal or distal or proximal or tubul*) NEAR/2 acidosis):ti,ab
#19	(hyperuricaemi* or hyperuricemi*):ti,ab
#20	MeSH descriptor Hyperuricemia, this term only
#21	MeSH descriptor Hyperparathyroidism, Secondary explode all trees
#22	(renal NEAR/2 (osteo* or hyperparathyroidism)):ti,ab
#23	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24	MeSH descriptor Ureteral Obstruction, this term only
#25	MeSH descriptor Urethral Obstruction explode all trees
#26	((uropath* or ureter* or urethra*) NEXT obstruct*):ti,ab
#27	(#24 OR #25 OR #26)
#28	(renal of kidney* or chronic):ti,ab
#29	(#27 AND #28)
#30	(#23 OR #29)
#31	(transplant* or donor* or graft* or allograft* or pregnan*):ti
#32	MeSH descriptor Renal Dialysis, this term only
#33	(predialysis or "pre dialysis" or ("not" NEAR/4 dialysis)):ti
#34	(#32 AND NOT #33)
#35	(#30 AND NOT (#31 OR #34))

F.2 Study filter search terms

F.2.1 Systematic review (SR) search terms

Medline search terms

1	meta-analysis/
2	meta-analysis as topic/
3	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

F.2.2 Randomised controlled studies (RCT) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.

5	randomly.ab.
6	clinical trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

F.2.3 Observational studies search terms

Medline search terms

1	exp cohort studies/
2	cross-sectional studies/
3	((prospective or cross sectional or follow up or longitudinal or comparative) and (study or studies or review or analys*)).ti,ab.
4	comparative study.pt.
5	(cohort* or participant*).ti,ab.
6	or/1-5

Embase search terms

1	comparative study/
2	longitudinal study/
3	prospective study/
4	cross-sectional study/
5	cohort analysis/
6	((prospective or cross sectional or follow up or longitudinal or comparative) and (study or studies or review or analys*)).ti,ab.
7	(cohort* or participant*).ti,ab.
8	or/1-7

F.2.4 Exclusions search terms

These terms were combined with searches using the NOT Boolean operator, in order to exclude unwanted study types such as animal studies.

Medline search terms

1	letter/
2	editorial/
3	news/
4	exp historical article/
5	anecdotes as topic/
6	comment/
7	case report/
8	(letter or comment*).ti.
9	or/1-8
10	9 not (randomized controlled trial/ or random*.ti,ab.)
11	animals/ not humans/
12	exp animals, laboratory/
13	exp animal experimentation/
14	exp models, animal/
15	exp rodentia/
16	(rat or rats or mouse or mice).ti.
17	or/10-16

Embase search terms

1	letter.pt. or letter/
2	note.pt.
3	editorial.pt.
4	case report/ or case study/
5	(letter or comment*).ti.
6	or/1-5
7	6 not (randomized controlled trial/ or random*.ti,ab.)
8	animal/ not human/
9	nonhuman/
10	exp animal experiment/
11	exp experimental animal/
12	animal model/
13	exp rodent/
14	(rat or rats or mouse or mice).ti.
15	or/7-14

F.2.5 Health economic search terms

Medline search terms

1	economics/

2	value of life/
3	exp "costs and cost analysis"/
4	exp economics, hospital/
5	exp economics, medical/
6	economics, nursing/
7	economics, pharmaceutical/
8	exp "fees and charges"/
9	exp budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	health economics/
2	exp economic evaluation/
3	exp health care cost/
4	exp fee/
5	budget/
6	funding/
7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

F.2.6 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.

6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroqol* or eq5d* or eq 5*).ti,ab.
8	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.
12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

Embase search terms

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroqol* or eq5d* or eq 5*).ti,ab.
10	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.
13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

F.3 Searches by specific questions

F.3.1 Measures and markers

Searches for the following two questions were run as one search:

What is the accuracy of equations to estimate GFR as a measurement of kidney function?

What is the best combination of measures of kidney function and markers of kidney damage to identify people with CKD who are at increased risk of progression?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Kidneys *Population terms in section F.1 not used. See below for all search terms:*	Measures and markers		SR, Observational NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Medline search terms

1	exp kidney diseases/ or exp kidney function tests/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	1 or 2
4	(transplant* or graft* or allograft* or pregnan*).ti.
5	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
6	3 not (4 or 5)
7	glomerular filtration rate/
8	glomerul* filtration rate.ti,ab.
9	(eGFR* or GFR*).ti,ab.
10	or/7-9
11	6 and 10
12	(formula* or equation* or reclassif* or re classif*).ti,ab.
13	(chronic kidney disease epidemiology collaboration or CKD EPI*).ti,ab.
14	(modif* of diet in renal disease* or MDRD*).ti,ab.
15	(multimark* or multi-mark* or multi* mark*).ti,ab.
16	or/12-15
17	11 and 16
18	cystatin c/
19	creatinine/
20	(creatinine or cystatin c or acr).ti,ab.

21	or/18-20
22	17 and 21
23	exp "sensitivity and specificity"/
24	disease progression/
25	prognosis/
26	risk/
27	risk factors/
28	(sensitivity or specificity or precision or bias).ti,ab.
29	(predict* or diagnos* or detect* or performance or accura* or risk* or prognos* or progression or PPV or NPV).ti,ab.
30	(reference or gold standard*).ti,ab.
31	or/23-30
32	22 and 31

Embase search terms

1	exp kidney disease/ or exp kidney function test/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	1 or 2
4	(transplant* or graft* or allograft* or pregnan*).ti.
5	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
6	3 not (4 or 5)
7	glomerulus filtration rate/
8	glomerul* filtration rate.ti,ab.
9	(eGFR* or GFR*).ti,ab.
10	or/7-9
11	6 and 10
12	(formula* or equation* or reclassif* or re classif*).ti,ab.
13	(chronic kidney disease epidemiology collaboration or CKD EPI*).ti,ab.
14	(modif* of diet in renal disease* or MDRD*).ti,ab.
15	(multimark* or multi-mark* or multi* mark*).ti,ab.
16	or/12-15
17	11 and 17
18	cystatin C/
19	(cystatin c or acr).ti,ab.
20	creatinine.ti,ab,hw.
21	or/18-20
22	17 and 21
23	"sensitivity and specificity"/
24	predictive value/

25	diagnostic accuracy/
26	diagnostic test accuracy study/
27	risk factor/
28	disease course/
29	disease exacerbation/
30	(predict* or diagnos* or detect* or performance or accura* or risk* or prognos* or progression or PPV or NPV).ti,ab.
31	(sensitivity or specificity or precision or bias).ti,ab.
32	(reference or gold standard*).ti,ab.
33	or/23-32
34	22 and 34

Cochrane search terms

#1	MeSH descriptor: [Kidney Diseases] explode all trees
#2	MeSH descriptor: [Kidney Function Tests] explode all trees
#3	MeSH descriptor: [Kidney] explode all trees
#4	(kidney* or renal or CKD):ti,ab
#5	#1 or #2 or #3 or #4
#6	(transplant* or graft* or allograft* or pregnan*):ti
#7	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*):ti
#8	#5 not (#6 or #7)
#9	MeSH descriptor: [Glomerular Filtration Rate] this term only
#10	(glomerul* next filtration next rate*):ti,ab
#11	(eGFR* or GFR*):ti,ab
#12	#9 or #10 or #11
#13	#8 and #12
#14	(formula* or equation* or reclassif* or “re classification” or “re classify” or “re classified”):ti,ab
#15	(“chronic kidney disease epidemiology collaboration”):ti,ab
#16	(CKD next EPI*):ti,ab
#17	(“modification of diet in renal disease” or “modifying of diet in renal disease” or MDRD*):ti,ab
#18	#14 or #15 or #16 or #17
#19	#13 and #18
#20	MeSH descriptor: [Cystatin C] this term only
#21	MeSH descriptor: [Creatinine] this term only
#22	(creatinine or “cystatin c” or acr):ti,ab
#23	#20 or #21 or #22
#24	#19 and #23
#25	MeSH descriptor: [Sensitivity and Specificity] explode all trees
#26	MeSH descriptor: [Disease Progression] this term only

#27	MeSH descriptor: [Prognosis] this term only
#28	MeSH descriptor: [Risk] this term only
#29	MeSH descriptor: [Risk Factors] this term only
#30	(sensitivity or specificity or precision or bias):ti,ab
#31	(predict* or diagnos* or detect* or performance or accura* or risk* or prognos* or progression or PPV or NPV):ti,ab
#32	(reference or "gold standard"):ti,ab
#33	#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34	#24 and #33

F.3.2 Classification

For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes (CKD progression, AKI, all-cause mortality and cardiovascular mortality)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Kidneys *Population terms in section F.1 not used. See below for all search terms:*	Proteinuria		SR, Observational NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Medline search terms

1	exp kidney diseases/ or exp kidney function tests/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	1 or 2
4	(transplant* or graft* or allograft* or pregnan*).ti.
5	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
6	3 not (4 or 5)
7	glomerular filtration rate/
8	glomerul* filtration rate.ti,ab.
9	(eGFR* or GFR*).ti,ab.
10	or/7-9
11	6 and 10
12	exp Proteinuria/
13	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
14	(PCR* or ACR* or UACR* or UPCR* proteinuria or albuminuria or microalbuminuria).ti,ab.
15	or/12-14
16	11 and 15
17	disease progression/

18	prognosis/
19	risk/
20	risk factors/
21	(predict* or diagnos* or risk* or hazard or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
22	or/17-21
23	16 and 22

Embase search terms

1	exp kidney disease/ or exp kidney function test/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	1 or 2
4	(transplant* or graft* or allograft* or pregnan*).ti.
5	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
6	3 not (4 or 5)
7	glomerulus filtration rate/
8	glomerul* filtration rate.ti,ab.
9	(eGFR* or GFR*).ti,ab.
10	or/7-9
11	6 and 10
12	exp proteinuria/
13	(PCR* or ACR* or UACR* or UPCR*).ti,ab.
14	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
15	(proteinuria or albuminuria or microalbuminuria).ti,ab.
16	or/12-15
17	11 and 16
18	prognosis/
19	risk factor/
20	disease course/
21	disease exacerbation/
22	(predict* or diagnos* or risk* or hazard or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
23	or/18-22
24	17 and 23

Cochrane search terms

#1	MeSH descriptor: [Kidney Diseases] explode all trees
#2	MeSH descriptor: [Kidney Function Tests] explode all trees
#3	MeSH descriptor: [Kidney] explode all trees
#4	(kidney* or renal or CKD):ti,ab

#5	#1 or #2 or #3 or #4
#6	(transplant* or graft* or allograft* or pregnan*):ti
#7	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*):ti
#8	#5 not (#6 or #7)
#9	MeSH descriptor: [Glomerular Filtration Rate] this term only
#10	(glomerul* next filtration next rate*):ti,ab
#11	(eGFR* or GFR*):ti,ab
#12	#9 or #10 or #11
#13	#8 and #12
#14	MeSH descriptor: [Proteinuria] explode all trees
#15	((urin* or ratio*) near/5 (albumin* or protein*)):ti,ab
#16	(proteinuria or albuminuria or microalbuminuria or PCR* or ACR* or UPCR* or UACR*):ti,ab
#17	#14 or #15 or #16
#18	#13 and #17
#19	MeSH descriptor: [Disease Progression] this term only
#20	MeSH descriptor: [Prognosis] this term only
#21	MeSH descriptor: [Risk] this term only
#22	MeSH descriptor: [Risk Factors] this term only
#23	(predict* or diagnos* or risk* or hazard or prognos* or progress* or PPV or NPV or death* or mortality):ti,ab
#24	#19 or #20 or #21 or #22 or #23
#25	#18 and #24

F.3.3 Cause – AKI

Searches for the following two questions were run as one search:

For people with CKD, does the presence of acute kidney injury (AKI) have an effect on adverse outcomes at any given category of eGFR and ACR (CKD progression, all-cause mortality and cardiovascular mortality)?

What is the risk of developing and/or progression of CKD after an episode of AKI?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	AKI		SR, Observational NOT Exclusions (Medline and Embase only)	Search run from 2002 up to 25 November 2013.

AKI search terms

Medline search terms

1	exp acute kidney injury/
2	AKI.ti,ab.
3	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
4	or/1-3
5	glomerular filtration rate/
6	glomerul* filtration rate.ti,ab.
7	(eGFR* or GFR*).ti,ab.
8	exp proteinuria/
9	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
10	(PCR* or ACR* or UACR* or UPCR* or proteinuria or albuminuria or microalbuminuria).ti,ab.
11	or/5-10
12	4 and 11
13	disease progression/
14	prognosis/
15	risk/
16	risk factors/
17	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
18	or/13-17
19	12 and 18

Embase search terms

1	acute kidney failure/ or acute kidney tubule necrosis/
2	((acute or early) adj (kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
3	AKI.ti,ab.
4	kidney injury/ and acute.ti,ab.
5	or/1-4
6	glomerulus filtration rate/
7	exp proteinuria/
8	glomerul* filtration rate.ti,ab.
9	(eGFR* or GFR*).ti,ab.
10	(PCR* or ACR* or UACR* or UPCR*).ti,ab.
11	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
12	(proteinuria or albuminuria or microalbuminuria).ti,ab.
13	or/6-12
14	5 and 13
15	prognosis/
16	risk factor/
17	disease course/

18	disease exacerbation/
19	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
20	or/15-19
21	14 and 20

Cochrane search terms

#1	MeSH descriptor: [Acute Kidney Injury] explode all trees
#2	AKI:ti,ab
#3	((acute or early) next (kidney or renal) next (failure* or injur* or insufficien* or dysfunction* or impair*)):ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Glomerular Filtration Rate] explode all trees
#6	MeSH descriptor: [Proteinuria] explode all trees
#7	(glomerul* next filtration next rate*):ti,ab
#8	(eGFR* or GFR*):ti,ab
#9	((urin* or ratio*) near/5 (albumin* or protein*)):ti,ab
#10	(proteinuria or albuminuria or microalbuminuria or PCR* or ACR* or UPCR* or UACR*):ti,ab
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11
#13	MeSH descriptor: [Disease Progression] this term only
#14	MeSH descriptor: [Prognosis] this term only
#15	MeSH descriptor: [Risk] this term only
#16	MeSH descriptor: [Risk Factors] this term only
#17	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality):ti,ab
#18	#13 or #14 or #15 or #16 or #17
#19	#12 and #18

F.3.4 Cause – glomerular disease

For people with CKD, does the presence of glomerular disease have an effect on adverse outcomes at any given category of eGFR and ACR (CKD progression, AKI, all-cause mortality and cardiovascular mortality)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Glomerular disease		SR, Observational NOT Exclusions (Medline and Embase only)	Search run from 2002 up to 25 November 2013.

Glomerular disease search terms

Medline search terms

1	exp glomerulonephritis/
2	nephrosis, lipoid/
3	((inflam* or disease) adj2 glomerul*).ti,ab.
4	(glomerulosclero* or glomerul* sclero* or glomerulonephr* or glomerul* nephr* or glomerulopath* or glomerulitis).ti,ab.
5	((glomerular or segmental) adj2 hyalino*).ti,ab.
6	((iga or immunoglobin a or membran* or lupus or minim* change or lipoid) adj2 (nephro* or nephriti*)).ti,ab.
7	((dense deposit or bright* or b?erger* or minim* change or basement membrane) adj disease*).ti,ab.
8	or/1-7
9	glomerular filtration rate/
10	glomerul* filtration rate.ti,ab.
11	(eGFR* or GFR*).ti,ab.
12	exp proteinuria/
13	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
14	(PCR* or ACR* or UACR* or UPCR* or proteinuria or albuminuria or microalbuminuria).ti,ab.
15	or/9-14
16	8 and 15
17	disease progression/
18	prognosis/
19	risk/
20	risk factors/
21	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
22	or/17-21
23	16 and 22
24	(gene* or genome* or serum or plasma or polymorphism* or allel* or effect of or effects of or dose* or dosage* or therap* or drug* or excretion or receptor* or smoking or weight or obesity or obese or exercise or activity or agent* or marker* or biomarker*).ti.
25	23 not 24

Embase search terms

1	exp glomerulonephritis/
2	glomerulopathy/
3	immunoglobulin a nephropathy/
4	glomerulosclerosis/
5	focal glomerulosclerosis/
6	lipoid nephrosis/
7	((inflam* or disease) adj2 glomerul*).ti,ab.
8	(glomerulosclero* or glomerul* sclero* or glomerulonephr* or glomerul* nephr* or

	glomerulopath* or glomerulitis).ti,ab.
9	((glomerular or segmental) adj2 hyalino*).ti,ab.
10	((iga or immunoglobin a or membran* or lupus or minim* change or lipoid) adj2 (nephro* or nephriti*)).ti,ab.
11	((dense deposit or bright* or b?erger* or minim* change or basement membrane) adj disease*).ti,ab.
12	or/1-11
13	glomerulus filtration rate/
14	exp proteinuria/
15	glomerul* filtration rate.ti,ab.
16	(eGFR* or GFR*).ti,ab.
17	(PCR* or ACR* or UACR* or UPCR*).ti,ab.
18	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
19	(proteinuria or albuminuria or microalbuminuria).ti,ab.
20	or/13-19
21	12 and 20
22	prognosis/
23	risk factor/
24	disease course/
25	disease exacerbation/
26	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality).ti,ab.
27	or/22-26
28	21 and 27
29	(gene* or genome* or serum or plasma or polymorphism* or allel* or effect of or effects of or dose* or dosage* or therap* or drug* or excretion or receptor* or smoking or weight or obesity or obese or exercise or activity or agent* or marker* or biomarker*).ti.
30	28 not 29

Cochrane search terms

#1	MeSH descriptor: [Glomerulonephritis] explode all trees
#2	MeSH descriptor: [Nephrosis, Lipoid] explode all trees
#3	((inflammation or disease) near/2 (glomerulus or glomerular)):ti,ab
#4	((glomerulo or glomerulus or glomerular) near/2 (sclerosis or scleroses or nephritis or nephritides or nephrosis or nephroses or nephropathy or nephropathies)):ti,ab
#5	(glomerulosclero* or glomerulonephr* or glomerulopath* or glomerulitis):ti,ab
#6	((glomerular or segmental) near/2 hyalinosis):ti,ab
#7	((iga or “immunoglobin a” or membranous or lupus or “minimal change” or “minimum change” or lipoid) near/2 (nephritis or nephritides or nephrosis or nephroses or nephrotic or nephropathy or nephropathies or nephro)):ti,ab
#8	((“dense deposit” or brights or bright or buerger or berger or “minimal change” or “minimum change” or “basement membrane”) next (disease or diseases)):ti,ab

#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [Glomerular Filtration Rate] this term only
#11	MeSH descriptor: [Proteinuria] explode all trees
#12	(glomerul* next filtration next rate*):ti,ab
#13	(eGFR* or GFR*):ti,ab
#14	((urin* or ratio*) near/5 (albumin* or protein*)):ti,ab
#15	(proteinuria or albuminuria or microalbuminuria or PCR* or ACR* or UPCR* or UACR*):ti,ab
#16	#10 or #11 or #12 or #13 or #14 or #15
#17	#9 and #16
#18	MeSH descriptor: [Disease Progression] this term only
#19	MeSH descriptor: [Prognosis] this term only
#20	MeSH descriptor: [Risk] this term only
#21	MeSH descriptor: [Risk Factors] this term only
#22	(predict* or risk* or hazard* or prognos* or progress* or PPV or NPV or death* or mortality):ti,ab
#23	#18 or #19 or #20 or #21 or #22
#24	#17 and #23
#25	(gene* or genome* or serum or plasma or polymorphism* or allel* or effect of or effects of or dose* or dosage* or therap* or drug* or excretion or receptor* or smoking or weight or obesity or obese or exercise or activity or agent* or marker* or biomarker*):ti
#26	#24 not #25

F.3.5 Cause – diabetes and hypertension

IPD analyses[208,411] were found from the Classification search that answered the following two questions; no additional searches were undertaken:

For people with CKD, does the presence of diabetes have an effect on adverse outcomes at any given category of eGFR and ACR (CKD progression, AKI, all-cause mortality and cardiovascular mortality)?

For people with CKD, does the presence of hypertension have an effect on adverse outcomes at any given category of eGFR and ACR (CKD progression, AKI, all-cause mortality and cardiovascular mortality)?

F.3.6 Frequency of monitoring

How frequently should eGFR, ACR or PCR be monitored in people with CKD?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Monitoring		SR, Observational NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Monitoring search terms

Medline search terms

1	glomerular filtration rate/
2	exp proteinuria/
3	glomerul* filtration rate*.ti,ab.
4	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
5	(eGFR* or GFR* or PCR* or ACR* or UACR* or UPCR* proteinuria or albuminuria or microalbuminuria).ti,ab.
6	or/1-5
7	disease progression/
8	monitor*.ti.
9	6 and (7 or 8)
10	prognosis/
11	time factors/
12	((interval* or every) adj5 (month* or year* or week*)).ti,ab.
13	(treatment adj3 (nonresponse* or failure* or response* or duration or outcome*)).ti,ab,hw.
14	(predict* adj2 (value* or treatment* or response* or outcome* or factor*)).ti,ab,hw.
15	((review* or recall* or follow up* or regular* or periodic*) adj3 (interval* or visit* or examin* or attend* or test*)).ti,ab.
16	(management adj (strateg* or protocol* or plan*)).ti,ab.
17	natural histor*.ti,ab.
18	(PPV or NPV).ti,ab.
19	or/10-18
20	monitor*.ab,hw.
21	19 and 20
22	6 and 21
23	9 or 22

Embase search terms

1	glomerulus filtration rate/
2	exp proteinuria/
3	glomerul* filtration rate*.ti,ab.
4	(PCR* or ACR* or UACR* or UPCR* or eGFR* or GFR*).ti,ab.
5	((urin* or ratio*) adj5 (albumin* or protein*)).ti,ab.
6	(proteinuria or albuminuria or microalbuminuria).ti,ab.
7	or/1-6
8	disease course/
9	disease exacerbation/
10	monitor*.ti.
11	or/8-10
12	7 and 11

13	therapy delay/
14	prognosis/
15	((interval* or every) adj5 (month* or year* or week*)).ti,ab.
16	(treatment adj3 (nonresponse* or failure* or response* or duration or outcome* or planning)).ti,ab,hw.
17	(predict* adj2 (value* or treatment* or response* or outcome* or factor*)).ti,ab,hw.
18	((review* or recall* or follow up* or regular* or periodic*) adj3 (interval* or visit* or examin* or attend* or test*)).ti,ab.
19	(PPV or NPV).ti,ab.
20	(management adj (strateg* or protocol* or plan*)).ti,ab.
21	natural histor*.ti,ab.
22	or/13-21
23	monitor*.ab,hw.
24	22 and 23
25	7 and 24
26	12 or 25

Cochrane search terms

#1	MeSH descriptor: [Glomerular Filtration Rate] this term only
#2	MeSH descriptor: [Proteinuria] explode all trees
#3	(glomerul* next filtration next rate*):ti,ab
#4	((urin* or ratio*) near/5 (albumin* or protein*)):ti,ab
#5	(proteinuria or albuminuria or microalbuminuria or PCR* or ACR* or UPCR* or UACR* or eGFR* or GFR*):ti,ab
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Disease Progression] this term only
#8	monitor*:ti
#9	#7 or #8
#10	#6 and #9
#11	MeSH descriptor: [Time Factors] this term only
#12	MeSH descriptor: [Predictive Value of Tests] this term only
#13	MeSH descriptor: [Prognosis] this term only
#14	((interval* or every) near/5 (month* or year* or week*)):ti,ab
#15	(treatment near/3 (nonresponse* or failure* or response* or duration or outcome*)):ti,ab
#16	((review* or recall* or "follow up" or regular* or periodic*) near/3 (interval* or visit* or examin* or attend* or test*)):ti,ab
#17	(predict* near/2 (treatment* or response* or outcome* or factor* or value*)):ti,ab
#18	(PPV or NPV):ti,ab
#19	(management next (strateg* or protocol* or plan*)):ti,ab
#20	(natural next histor*):ti,ab
#21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22	monitor*:ab
#23	MeSH descriptor: [Monitoring, Physiologic] explode all trees
#24	#22 or #23
#25	#21 and #24
#26	#11 or #25

F.3.7 Low protein diet

For people with CKD, are low protein diets a clinically and cost effective method for the management of CKD?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Low protein diet		SR, RCT NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Low protein diet search terms

Medline search terms

1	exp proteins/ and exp diet therapy/
2	diet, protein-restricted/
3	exp dietary proteins/
4	((protein or proteins) adj5 (low or intake* or restrict* or consum* or reduc* or diet*)).ti,ab.
5	hypoproteic.ti,ab.
6	or/1-5

Embase search terms

1	diet restriction/ or diet therapy/
2	protein/
3	1 and 2
4	protein restriction/
5	protein diet/
6	protein intake/
7	((protein or proteins) adj5 (low or intake* or restrict* or consum* or reduc* or diet*)).ti,ab.
8	hypoproteic.ti,ab.
9	or/3-8

Cochrane search terms

#1	MeSH descriptor Proteins explode all trees
#2	MeSH descriptor Diet Therapy explode all trees
#3	(#1 AND #2)

#4	MeSH descriptor Diet, Protein-Restricted, this term only
#5	MeSH descriptor Dietary Proteins explode all trees
#6	((protein or proteins) NEAR/5 (low or intake* or restrict* or consum* or reduc* or diet*)):ti,ab
#7	hypoproteic:ti,ab
#8	(#3 OR #4 OR #5 OR #6 OR #7)

F.3.8 Self management support systems

For people with CKD, what is the clinical and cost effectiveness of self management support systems?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Self management support systems		NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Medline search terms

1	exp self care/
2	patient education as topic/
3	telemedicine/
4	publications/
5	pamphlets/
6	internet/
7	access to information/
8	consumer health information/
9	information dissemination/
10	patient preference/
11	disease management/
12	(self adj3 (manag* or care)).ti,ab.
13	((train* or teach* or educat*) adj3 (model* or program* or structured or intervention* or support)).ti,ab.
14	(patient* adj3 (information* or educat* or knowledge or literacy or learn* or train* or program* or prefer* or expectation*)).ti,ab.
15	(information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
16	(decision adj5 (aid* or tool*)).ti,ab.
17	(patient* adj3 (literature or leaflet* or booklet* or pamphlet* or handout* or internet or website* or interview* or survey*)).ti,ab.
18	Focus groups/
19	or/1-18

Embase search terms

1	exp self care/

2	exp telehealth/
3	publication/
4	internet/
5	patient decision making/
6	patient preference/
7	access to information/
8	consumer health information/
9	information dissemination/
10	patient education/
11	(self adj3 (manag* or care)).ti,ab.
12	((train* or teach* or educat*) adj3 (model* or program* or structured or intervention* or support)).ti,ab.
13	(patient* adj3 (information* or educat* or knowledge or literacy or learn* or train* or program* or prefer* or expectation*)).ti,ab.
14	(information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
15	(patient* adj3 (literature or leaflet* or booklet* or pamphlet* or handout* or internet or website* or interview* or survey*)).ti,ab.
16	(decision adj5 (aid* or tool*)).ti,ab.
17	or/1-16

Cochrane search terms

#1	MeSH descriptor Self Care explode all trees
#2	MeSH descriptor Patient Education as Topic, this term only
#3	MeSH descriptor Telemedicine, this term only
#4	MeSH descriptor Publications, this term only
#5	MeSH descriptor Pamphlets, this term only
#6	MeSH descriptor Internet, this term only
#7	MeSH descriptor Access to Information, this term only
#8	MeSH descriptor Consumer Health Information explode all trees
#9	MeSH descriptor Information Dissemination, this term only
#10	MeSH descriptor Patient Preference explode all trees
#11	MeSH descriptor Disease Management, this term only
#12	(self NEAR/3 (manag* or care)):ti,ab
#13	((train* or teach* or educat*) NEAR/3 (model* or program* or structured or intervention* or support)):ti,ab
#14	(patient* NEAR/3 (information* or educat* or knowledge or literacy or learn* or train* or program* or prefer* or expectation*)):ti,ab
#15	(information* NEAR/3 (need* or requirement* or support* or seek* or access* or disseminat*)):ti,ab
#16	(patient* NEAR/3 (literature or leaflet* or booklet* or pamphlet* or handout* or internet or website* or interview* or survey*)):ti,ab

#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

F.3.9 Renin-angiotensin-aldosterone system antagonists

For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone system antagonists in the management of CKD?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	RAAS		RCT NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

RAAS search terms

Medline search terms

1	angiotensin-converting enzyme inhibitors/
2	angiotensin ii type 1 receptor blockers/
3	angiotensin ii type 2 receptor blockers/
4	aldosterone antagonists/
5	((angiotensin* or renin or aldosterone or ace) adj5 (antagonist* or blocker* or inhibitor*)).ti,ab.
6	(RAAS or RAS or RASI or ARB or ARBs).ti,ab.
7	exp enalapril/
8	fosinopril/
9	lisinopril/
10	perindopril/
11	ramipril/
12	captopril/
13	(enalapril* or fosinopril* or lisinopril*or perindopril* or quinapril* or ramipril* or cilizapril* or captopril* or trandolapril* or imidapril* or moexipril*).ti,ab.
14	(innovace* or innozide* or zestril* or carace* or zestoretic* or coversyl* or accupro* or accuretic* or tritace* or triapin* or vascace* or capoten* or capozide* or cozidocapt* or zidocapt* or gopten* or tarka* or tanatril* or perdix*).ti,ab.
15	spironolactone/
16	(eplerenone* or spironolactone* or aliskiren*).ti,ab.
17	(inspra* or aldactone* or coflumactone* or flumactone* or lasilactone* or rasilez*).ti,ab.
18	losartan/
19	(candesartan* or azilsartan* or eprosartan* or irbesartan* or losartan* or olmesartan* or telmisartan*).ti,ab.
20	(amias* or atacand* or edarbi* or teveten* or aprovel* or coaprovel* or cozaar* or olmetec* or benicar* or sevikar* or micardis* or diovan* or codiovan*).ti,ab.

21	or/1-20

Embase search terms

1	*dipeptidyl carboxypeptidase inhibitor/
2	angiotensin receptor antagonist/
3	aldosterone antagonist/
4	renin inhibitor/
5	((angiotensin* or renin or aldosterone or ACE) adj5 (antagonist* or blocker* or inhibitor*)).ti,ab.
6	enalapril maleate/ or fosinopril/ or lisinopril/ or perindopril/ or quinapril/ or ramipril/ or captopril/ or trandolapril/ or imidapril/ or moexipril/
7	(enalapril* or fosinopril* or lisinopril*or perindopril* or quinapril* or ramipril* or cilizapril* or captopril* or trandolapril* or imidapril* or moexipril*).ti,ab.
8	(innovace* or innozide* or zestril* or carace* or zestoretic* or coversyl* or accupro* or accuretic* or tritace* or triapin* or vascace* or capoten* or capozide* or cozidocapt* or zidocapt* or gopten* or tarka* or tanatril* or perdix*).ti,ab.
9	eplerenone/
10	spironolactone/
11	aliskiren/
12	(eplerenone* or spironolactone* or aliskiren*).ti,ab.
13	(inspra* or aldactone* or coflumactone* or flumactone* or lasilactone* or rasilez*).ti,ab.
14	candesartan/ or azilsartan/ or eprosartan/ or irbesartan/ or losartan potassium/ or olmesartan/ or telmisartan/
15	(candesartan* or azilsartan* or eprosartan* or irbesartan* or losartan* or olmesartan* or telmisartan*).ti,ab.
16	(amias* or atacand* or edarbi* or teveten* or aprovel* or coaprovel* or cozaar* or olmetec* or benicar* or sevikar* or micardis* or diovan* or codiovan*).ti,ab.
17	or/1-16

Cochrane search terms

#1	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] this term only
#2	MeSH descriptor: [Angiotensin II Type 1 Receptor Blockers] this term only
#3	MeSH descriptor: [Angiotensin II Type 2 Receptor Blockers] this term only
#4	MeSH descriptor: [Aldosterone Antagonists] this term only
#5	((angiotensin* or renin or aldosterone or ACE) near/5 (antagonist* or blocker* or inhibitor*)):ti,ab
#6	(RAAS or RAS or RASI or ARB or ARBs):ti,ab
#7	MeSH descriptor: [Enalapril] explode all trees
#8	MeSH descriptor: [Fosinopril] this term only
#9	MeSH descriptor: [Lisinopril] this term only
#10	MeSH descriptor: [Perindopril] this term only
#11	MeSH descriptor: [Ramipril] this term only

#12	MeSH descriptor: [Captopril] this term only
#13	(enalapril* or fosinopril* or lisinopril*or perindopril* or quinapril* or ramipril* or cilizapril* or captopril* or trandolapril* or imidapril* or moexipril*):ti,ab
#14	(innovace* or innozide* or zestril* or carace* or zestoretic* or coversyl* or accupro* or accuretic* or tritace* or triapin* or vascace* or capoten* or capozide* or cozidocapt* or zidocapt* or gopten* or tarka* or tanatril* or perdix*):ti,ab
#15	MeSH descriptor: [Spironolactone] this term only
#16	(eplerenone* or spironolactone* or aliskiren*):ti,ab
#17	(inspra* or aldactone* or coflumactone* or flumactone* or lasilactone* or rasilez*):ti,ab
#18	MeSH descriptor: [Losartan] this term only
#19	(candesartan* or azilsartan* or eprosartan* or irbesartan* or losartan* or olmesartan* or telmisartan*):ti,ab
#20	(amias* or atacand* or edarbi* or teveten* or aprovel* or coaprovel* or cozaar* or olmetec* or benicar* or sevikar* or micardis* or diovan* or codiovan*):ti,ab
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

F.3.10 Antiplatelet and anticoagulant therapy

For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Kidneys *Population terms in section F.1 not used. See below for all search terms:*	Antiplatelets		SR, RCT NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Medline search terms

1	exp kidney diseases/ or exp kidney function tests/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	transplant*.ti.
4	(1 or 2) not 3
5	aspirin/
6	warfarin/
7	(acetylsalicylic acid* or aspirin* or apixaban* or rivaroxaban* or warfarin* or clopidogrel* or ticagrelor* or prasugrel* or dabigatran*).ti,ab.
8	(coumadin* or jantoven* or marevan* or lawarin* or waran* or warfant* or plavix* or brilique* or brilinta* or possia* or pradax* or prazaxa* or effient* or efient* or eliquis* or xarelto*).ti,ab.
9	or/5-8
10	4 and 9

Embase search terms

1	exp kidney disease/ or exp kidney function test/ or exp kidney/
2	(kidney* or renal or ckd).ti,ab.
3	transplant*.ti.
4	(1 or 2) not 3
5	*acetylsalicylic acid/
6	warfarin/
7	clopidogrel/
8	ticagrelor/
9	dabigatran/
10	dabigatran etexilate/
11	prasugrel/
12	apixaban/
13	rivaroxaban/
14	(acetylsalicylic acid* or aspirin* or apixaban* or rivaroxaban* or warfarin* or clopidogrel* or ticagrelor* or prasugrel* or dabigatran*).ti,ab.
15	(coumadin* or jantoven* or marevan* or lawarin* or waran* or warfant* or plavix* or brilique* or brilinta* or possia* or pradax* or prazaxa* or effient* or efient* or eliquis* or xarelto*).ti,ab.
16	or/5-15
17	4 and 16

Cochrane search terms

#1	MeSH descriptor: [Kidney Diseases] explode all trees
#2	MeSH descriptor: [Kidney Function Tests] explode all trees
#3	MeSH descriptor: [Kidney] explode all trees
#4	(kidney* or renal or CKD):ti,ab
#5	transplant*:ti
#6	(#1 or #2 or #3 or #4) not #5
#8	MeSH descriptor: [Aspirin] explode all trees
#9	MeSH descriptor: [Warfarin] explode all trees
#10	(“acetylsalicylic acid” or aspirin* or apixaban* or rivaroxaban* or warfarin* or clopidogrel* or ticagrelor* or prasugrel* or dabigatran*):ti,ab
#11	(coumadin* or jantoven* or marevan* or lawarin* or waran* or warfant* or plavix* or brilique* or brilinta* or possia* or pradax* or prazaxa* or effient* or efient* or eliquis* or xarelto*) .ti,ab.
#12	#8 or #9 or #10 or #11
#13	#6 and #12

F.3.11 Asymptomatic hyperuricaemia

For people with CKD and asymptomatic hyperuricaemia, what is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Allopurinol, febuxostat		SR, RCT NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Allopurinol, febuxostat search terms

Medline search terms

1	allopurinol/
2	(allopurinol* or purinol).ti,ab.
3	(febuxostat or adenuric or uloric).ti,ab.
4	or/1-3

Embase search terms

1	febuxostat/
2	(febuxostat or adenuric or uloric or purinol).ti,ab.
3	allopurinol*.ti,ab,hw.
4	or/1-3

Cochrane search terms

#1	MeSH descriptor Allopurinol, this term only
#2	(allopurinol* or purinol):ti,ab
#3	(febuxostat or adenuric or uloric):ti,ab
#4	(#1 OR #2 OR #3)

F.3.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

For people with GFR 15-60 ml/minml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Vitamin D		SR, RCT NOT Exclusions (Medline and Embase only)	Search run from 2007 up to 25 November 2013.

Vitamin D search terms

Medline search terms

1	exp vitamin d/
2	(vitamin adj (D or D2 or D3 or D4 or D5)).ti,ab.
3	(paracalcitol* or zemplar* or ergocalciferol* or alfacalcidol* or one-alpha* or calcitriol* or rocaltrol* or calcijex* or oxacalcitriol* or falecalcitriol* or fluorocalcitriol*).ti,ab.
4	(dihydrotachysterol* or maxacalcitol* or calciferol* or calcifediol* or doxercalciferol* or cholecalciferol* or ercalcidiol* or hectorol* or sitocalciferol* or paracalcin*).ti,ab.
5	(dihydroxyvitamin* or hydroxyvitamin* or hydroxycalciferol* or dihydroxycalciferol* or hydroxyergocalciferol* or dihydroxyergocalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol*).ti,ab.
6	or/1-5

Embase search terms

1	exp vitamin d/
2	(vitamin adj (D or D2 or D3 or D4 or D5)).ti,ab.
3	(paracalcitol* or zemplar* or ergocalciferol* or alfacalcidol* or one-alpha* or calcitriol* or rocaltrol* or calcijex* or oxacalcitriol* or falecalcitriol* or fluorocalcitriol*).ti,ab.
4	(dihydrotachysterol* or maxacalcitol* or calciferol* or calcifediol* or doxercalciferol* or cholecalciferol* or ercalcidiol* or hectorol* or sitocalciferol* or paracalcin*).ti,ab.
5	(dihydroxyvitamin* or hydroxyvitamin* or hydroxycalciferol* or dihydroxycalciferol* or hydroxyergocalciferol* or dihydroxyergocalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol*).ti,ab.
6	or/1-5

Cochrane search terms

#1	MeSH descriptor Vitamin D explode all trees
#2	(vitamin NEXT (D or D2 or D3 or D4 or D5)):ti,ab
#3	(paracalcitol* or zemplar* or ergocalciferol* or alfacalcidol* or one-alpha* or calcitriol* or rocaltrol* or calcijex* or oxacalcitriol* or falecalcitriol* or fluorocalcitriol*):ti,ab
#4	(dihydrotachysterol* or maxacalcitol* or calciferol* or calcifediol* or doxercalciferol* or cholecalciferol* or ercalcidiol* or hectorol* or sitocalciferol* or paracalcin*):ti,ab
#5	(dihydroxyvitamin* or hydroxyvitamin* or hydroxycalciferol* or dihydroxycalciferol* or hydroxyergocalciferol* or dihydroxyergocalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol*):ti,ab
#6	(#1 OR #2 OR #3 OR #4 OR #5)

F.3.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD	Bicarbonate		SR, RCT NOT Exclusions (Medline and Embase only)	Search run up to 25 November 2013. No start date restrictions.

Bicarbonate search terms

Medline search terms

1	exp bicarbonates/
2	bicarbonate*.ti,ab.
3	(hydrogen adj2 carbonate*).ti,ab.
4	or/1-3
5	((contrast or radiocontrast) and (nephropathy or induce*)).ti.
6	4 not 5

Embase search terms

1	exp bicarbonates/
2	bicarbonate*.ti,ab.
3	(hydrogen adj2 carbonate*).ti,ab.
4	or/1-3
5	((contrast or radiocontrast) and (nephropathy or induce*)).ti.
6	4 not 5

Cochrane search terms

#1	MeSH descriptor Bicarbonates explode all trees
#2	bicarbonate*:ti,ab
#3	(hydrogen near/2 carbonate*):ti,ab
#4	(#1 OR #2 OR #3)
#5	((contrast or radiocontrast) and (nephropathy or induce*)):ti
#6	(#4 AND NOT #5)

F.4 Economics search

F.4.1 Economics search

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD			Economic NOT Exclusions (Medline and Embase only).	Search run from 2009 in Medline and Embase, from 2007 in CRD and HEED, up to 25 November 2013.

CRD search terms

#1	MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES IN NHSEED,HTA
#2	MeSH DESCRIPTOR Kidney Diseases EXPLODE ALL TREES IN NHSEED,HTA
#3	(chronic) IN NHSEED, HTA
#4	#2 AND #3
#5	(((chronic or progressive) adj2 (renal or kidney))) IN NHSEED, HTA
#6	((chronic NEXT (kidney or renal) NEXT insufficienc*)) IN NHSEED, HTA
#7	(("end stage" adj2 (kidney or renal))) IN NHSEED, HTA
#8	((CKD or ESRD)) IN NHSEED, HTA
#9	MeSH DESCRIPTOR Diabetic Nephropathies IN NHSEED,HTA
#10	MeSH DESCRIPTOR Glomerulonephritis EXPLODE ALL TREES IN NHSEED,HTA
#11	MeSH DESCRIPTOR Proteinuria EXPLODE ALL TREES IN NHSEED,HTA
#12	MeSH DESCRIPTOR Acidosis, Renal Tubular IN NHSEED,HTA
#13	MeSH DESCRIPTOR Hypertension, Renal EXPLODE ALL TREES IN NHSEED,HTA
#14	((diabetic NEXT (kidney or renal) NEXT (disease* or failure))) IN NHSEED, HTA
#15	(((renal or renovascular) adj2 hypertensi*)) IN NHSEED, HTA
#16	((glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria*)) IN NHSEED, HTA
#17	((glomerular NEXT (sclerosis or nephritis))) IN NHSEED, HTA
#18	(((renal or distal or proximal) NEXT "tubular acidosis")) IN NHSEED, HTA
#19	("asymptomatic hyperuricaemia") IN NHSEED, HTA
#20	#1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

HEED search terms

1	AX=kidney or renal
2	AX=chronic
3	CS=1 AND 2
4	AX=CKD
5	CS=3 OR 4

F.4.2 Quality of life search

Quality of life searches were conducted in Medline and Embase

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
CKD			Quality of life NOT Exclusions	Search run from 2007 up to 25 November 2013.

Appendix G: Clinical evidence tables

G.1 Measuring kidney function

Table 18: BJORK 2012

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Bjork et al 2012[81] **Country:** Sweden	External validation; non-renal transplant patients aged ≥16 years; patients on dialysis excluded; 45% female; median age 61 years (range 19-83). **Patients**, n: 996 patients (1397 examinations)	Enzymatic method; Hitachi 911 analyser (May 2005 to June 2008) then (to December 2009) dry slide enzymatic method on a Vitrus 5.1 instrument (Ortho Clinical Diagnostics, Rochester, NY, USA); both used calibrator traceable to isotope dilution mass spectrometry (IDMS); negligible difference between	**Reference standard**: Iohexol clearance **Mean (SD) ml/minml/min/1.73m^2:** median 44 (range 12-116)	MDRD 175 x (sCr/ 88.4)$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female] x 1.210 [if African-American]	Accuracy (P30) [95% CI]	79.5 [77.3 to 81.6]	Data set included participants more than once so CIs may underestimate statistical uncertainty, P30 increased by 1-2% when multiple examinations excluded (not in results). 95% CI not reported for
					Bias [95% CI] (defined as the median difference [eGFR-mGFR] and median percentage difference)	-0.8 [-1.4 to -0.4] ml/minml/min/1.73m^2 and -2.2% [-3.3 to -0.9]	
					Precision [95% CI] (defined as IQR of differences eGFR-mGFR)	12.3 [11.5 to 13.2] ml/minml/min/1.73m^2	
					Sensitivity, Specificity, Area under the curve (AUC)	NR	
					Net Reclassification Index (NRI)	Overall 65% patients classified correctly, performed best at 30-59 ml/minml/min/1.73m^2 where 77% classified	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	Subgroups: GFR 60-89 ml/minml/min/1.73 m^2 n=313 GFR 30-59 n=414 ≥80 ml/minml/min/1.73 m^2 n=91	assays				correctly	subgroups. Bias and P30 also reported for GFR <15; 15-29; <30 and ≥90 ml/minml/min/1.73 m^2 P10 also reported overall and for all GFR subgroups.
				GFR 60-89ml/minml/min/1.73m^2	Accuracy (P30)	84%	
					Bias (median percentage difference)	-1%	
				GFR 30-59ml/minml/min/1.73m^2	Accuracy (P30)	93%	
					Bias (median percentage difference)	-8%	
				Age ≥ 80 years	Accuracy (P30)	67%	
					Bias (median percentage difference)	16%	
				CKD-EPI (for white or other non-black): female and sCr ≤62µmol/L: 144 x (sCr/ 62)$^{-0.329}$ x 0.993^{age} ; female and sCr >62µmol/L: 144 x (sCr/ 62)$^{-1.209}$ x 0.993^{age} ; male and sCr ≤80µmol/L: 141 x (sCr/ 80)$^{-0.411}$ x 0.993^{age} ; and male and sCr >80µmol/L: 141 x (sCr/ 80)$^{-1.209}$ x	Accuracy (P30) [95% CI]	79.1 [77.0 to 81.2]	
					Bias [95% CI] (defined as the median difference [eGFR-mGFR] and median percentage difference)	0.8 [0.2 to 1.3] ml/min/1.73m^2 and 1.7% [0.4 to 3.7]	
					Precision [95% CI]	11.7 [10.9 to 12.7] ml/min/1.73m^2	
					Sensitivity, Specificity, AUC	NR	
					Net Reclassification Index (NRI)	69% patients classified correctly, superior at >90ml/min/1.73m^2	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				0.993^{age}			
				GFR 60-89ml/min/1.73m^2	Accuracy (P30)	92%	
					Bias (median percentage difference)	0%	
				GFR 30-59ml/min/1.73m^2	Accuracy (P30)	79%	
					Bias (median percentage difference)	2%	
				Age ≥ 80 years	Accuracy (P30)	74%	
					Bias (median percentage difference)	11%	

Table 19: ILIADIS2011

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Iliadis et al 2011[292] **Country:**	Patients with type 2 diabetes; mean (SD) age 65 (10) years; 53% female; all	Serum creatinine measured by chemistry analyser (Cobas Integra 400, Roche, Rotkreutz,	**Reference standard**: ^{51}Cr-EDTA **Mean (SD)**	MDRD: 175 x (sCr/ 88.4)$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female]	Accuracy (P30) [95% CI]	78.8%	White people only, so unable to study different ethnicities;
					Bias [95% CI] (defined as the mean difference [eGFR-mGFR])	7.5	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Greece	Europids **Patients**, n: 448 (originally 460 but 12 patients with measured GFR <30ml/min/1.73 m^2 excluded) Subgroups: GFR <60 n=145 GFR <90 n=339 (includes GFR<60 ml/min/1.73 m^2 subgroup)	Switzerland); creatinine using Jaffe method standardised to IDMS.	**ml/min/1.73 m^2:** 73.4 (23.0)		Precision [95% CI] (defined as SD of bias)	13.4	small number of patients with measured GFR <30 ml/min/1.73m^2 so unable to study the performance of the equations in such patients. Cystatin C not standardised therefore not included in review.
					Sensitivity, specificity, AUC and NRI	NR	
				eGFR <60 ml/min/1.73 m^2	Sensitivity [95% CI]	86.5% [78.7-92.2]	
					Specificity [95% CI]	89.5% [85.0-93.0]	
					AUC [95% CI]	0.947 [0.917-0.968]	
				eGFR <90 ml/min/1.73 m^2	Sensitivity [95% CI]	73.9% [68.2-79.0]	
					Specificity [95% CI]	94.8% [88.3-98.3]	
					AUC [95% CI]	0.920 [0.887-0.947]	
				CKD-EPI female and sCr ≤62µmol/L: 144 x (sCr/ $62^{)-0.329}$ x 0.993^{age} ; female and sCr >62µmol/L: 144 x (sCr/ $62^{)-1.209}$ x 0.993^{age} ; male and sCr ≤80µmol/L: 141 x $(sCr/ 80)^{-0.411}$ x 0.993^{age} ; and male and sCr >80µmol/L: 141 x (sCr/ $80^{)-1.209}$ x 0.993^{age}	Accuracy (P30) [95% CI]	80.7%	
					Bias [95% CI]	7.1	
					Precision [95% CI]	12.0	
					Sensitivity, specificity, AUC and NRI	NR	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				eGFR <60 ml/min/1.73 m^2	Sensitivity [95% CI]	91.0% [84.1-95.6]	
					Specificity [95% CI]	88.3% [83.6-92.0]	
					AUC [95% CI]	0.952 [0.924-0.972]	
				eGFR <90 ml/min/1.73 m^2	Sensitivity [95% CI]	84.3% [79.4-88.5)	
					Specificity [95% CI]	91.7% [84.2-96.3]	
					AUC [95% CI]	0.937 [0.906-0.960]	

Table 20: INKER2012A

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Inker et al 2012[299] **Country:** USA	External validation set from 4 studies (NephroTest, Steno, RASS and Lund CKD), excluded renal transplant recipients. 53% diabetic, 3%	Roche enzymatic method (Roche–Hitachi P-Module with Roche Creatininase Plus assay), traceable to National Institute of Standards and Technology creatinine standard	**Reference standard**: Iothalomate and other filtration markers **Mean (SD) ml/min/1.73 m^2:**	CKD-EPI$_{cr}$ (creatinine based equation) female and sCr ≤0.7: $(sCr/0.7)^{-0.329}$ x 0.993^{age} x 144 [if white or other] or x 166 [if black]; female and sCr >0.7: $(sCr/0.7)^{-1.209}$ x 0.993^{age} x 144 [if	Accuracy (P30)* [95% CI]	87.2% [85.3-89.1]	*Accuracy reported as 1-P30; P30 calculated by NCGC. Also reports 1-P20. Accuracy, Bias
					Bias** [95% CI] (defined as the median difference [eGFR-mGFR])	-3.7[-4.6 to -2.8]	
					Precision [95% CI] (defined as IQR of differences mGFR-eGFR)	15.4 [14.3-16.5]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	black, age mean(SD) 50(17). **Patients**, n: 1119 (External validation set) Subgroups: eGFR 60-89 ml/min/1.73 m^2: n=215 eGFR <60 ml/min/1.73 m^2;n=533	reference material (SRM 967). Cystatin C calibrated on the Siemens Dade Behring Nephelometer, traceable to the Internation federation of Clinical Chemistry Working group for Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements certified reference materials.	70 (41)	white or other] or x 166 [if black]; male and sCr ≤0.9: $(sCr/0.9)^{-0.411}$ x 0.993^{age} x 141 [if white or other] or x 163 [if black]; and male and sCr >0.9: $(sCr/ 0.9)^{-1.209}$ x 0.993^{age} x 141 [if white or other] or x 163 [if black]			and Precision also reported for eGFR ≥90. **Bias reported as median difference [mGFR-eGFR]; median difference [eGFR-mGFR] calculated by NCGC.
					Sensitivity, Specificity and AUC and NRI	NR	
				eGFR 60-89ml/min/1.73m^2	Accuracy (P30) [95% CI]	89.8% [85.8-93.6]	
					Bias [95% CI]	-6.6 [-9.2 to -3.5]	
					Precision [95% CI]	19.6 [17.3-23.2]	
				eGFR <60 ml/min/1.73 m^2	Accuracy (P30) [95% CI]	83.4% [80.3-86.4]	
					Bias [95% CI]	-1.8 [-2.5 to -1.1]	
					Precision [95% CI]	10.0 [8.9-11.0]	
				CKD-EPIcys (cystatin C based equation) female or male and sCysC ≤0.8: 133 x $(sCysC/0.8)^{-0.499}$ x 0.996^{age} [x 0.932 if	Accuracy (P30) [95% CI]	85.9% [83.8-87.8]	
					Bias [95% CI]	-3.4 [-4.4 to -2.3]	
					Precision [95% CI]	16.4 [14.8-17.8]	
					Sensitivity, Specificity, AUC	NR	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				female]; female or male and sCysC >0.8: 133 x (sCysC/0.8)$^{-1.328}$ x 0.996^{age} [x 0.932 if female]	And NRI		
				eGFR 60-89ml/min/1.73m^2	Accuracy (P30) [95% CI]	87.3% [82.6-91.5]	
					Bias [95% CI]	-6.0 [-8.5 to -4.6]	
					Precision [95% CI]	19.6 [16.1-23.1]	
				eGFR <60 ml/min/1.73 m^2	Accuracy (P30) [95% CI]	78.6% [75.1-81.8]	
					Bias [95% CI]	-0.4 [-1.4to 0.5]	
					Precision [95% CI]	11.0 [10.0-12.4]	
				CKD-EPI$_{cr-cys}$ (creatinine and cystatin C based equation) 135 x min(Scr/κ, 1)$^{\alpha}$ x max(Scr/κ, 1)$^{-0.601}$ x min(Scys/0.8, 1)$^{-0.375}$ x max(Scys/0.8, 1)$^{-0711}$ 0.995^{Age} x 0.969 [if female] x 1.08 [if black] ml/min/1.73m^2 where κ=0.7 for	Accuracy (P30) [95% CI]	91.5% [89.8-93.0]	
					Bias [95% CI]	-3.9 [- 4.5 to -3.2]	
					Precision [95% CI]	13.4 [12.3-14.5]	
					Sensitivity, Specificity, AUC	NR	
					NRI [95% CI] (compared to CKD EPI sCr threshold eGFR<60 ml/min/1.73 m^2)	Overall: 4.9 [2.2-7.7] eGFR 45-74 ml/min/1.73 m^2: 19.4 [8.7-30.1]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				women and 0.9 for men, α is -0.248 for women and -0.207 for men, "min" indicates the minimum of Scr/κ or 1 and "max" is the maximum of Scr/κ or 1			
				eGFR 60-89 ml/min/1.73m^2	Accuracy (P30) [95% CI]	94.7% [91.8-97.3]	
					Bias [95% CI]	-6.9 [-8.9 to -5.0]	
					Precision [95% CI]	15.9 [13.9-18.1]	
				eGFR <60 ml/min/1.73 m^2	Accuracy (P30) [95% CI]	86.7% [83.9-89.3]	
					Bias [95% CI]	-1.3 [- 1.8 to -0.5]	
					Precision [95% CI]	8.1 [7.3-9.1]	

Table 21: KILBRIDE2013

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Kilbride et al 2013[341] **Country:** UK	People aged 74 years or older; known to the Kidney Care Centre or recruited from the community; excluded if history of reaction to iodinated contrast material, current active malignancy, life expectancy <3 months, cognitive impairment precluding consent, recent (<3 months) acute kidney injury, renal dialysis. Median	Plasma creatinine measured using modified stable isotope-dilution electrospray tandem mass spectrometric method (Applied Biosystems SCIEX API5000). Cystatin C measured by particle-enhanced nephelometric immunoassay using BN Prospec analyser (Siemens Healthcare Diagnostics)	**Reference standard**: Iohexol **Mean (SD) ml/min/1.73 m^2:** 53.4 (range 7.2-100.9)	IDMS traceable version of the 4-variable MDRD	Accuracy (P30) [95% CI]	81% [77-85]	All European ancestry so no analysis on other ethnicities. Also reports outcomes for age <80 years and ≥80 years.
					Bias [95% CI] (defined as the difference [eGFR-mGFR])	3.5 [1.9-4.8]	
					Precision [95% CI] (defined as RMSE and IQR of differences eGFR-mGFR)	RMSE:13.4 [11.8-14.9] IQR:13.7 [11.4-16.0]	
					Sensitivity, Specificity, AUC and NRI	NR	
				mGFR ≥60 ml/min/1.73m^2	Accuracy (P30) [95% CI]	86% [79-91]	
					Bias [95% CI]	5.5 [3.4 to 8.1]	
					Precision [95% CI])	RMSE: 16.2 [13.4-18.6] IQR:18.3 [14.3-22.3]	
				mGFR <60	Accuracy (P30) [95% CI]	78% [72-83]	
					Bias [95% CI]	2.0 [0.8to 3.9]	
					Precision [95% CI])	RMSE: 11.1 [9.5 -12.6] IQR: 11.4 [9.5 – 13.3]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	age 80 (range 74-97) years; 52% female; 19% diabetes. **Patients**, n: 394 (original sample also included 3 people of African-Caribbean ethnicity and 1 amputee but these were excluded). Subgroups: eGFR <60: n=234 eGFR ≥60; n=160			CKD-EPI$_{cr}$ (creatinine based equation)	Accuracy (P30) [95% CI]	83% [79-87]	
					Bias [95% CI]	1.7 [0.3-3.2]	
					Precision [95% CI]	RMSE:10.9 [10.0-11.7] IQR:13.1 [11.7-14.6]	
					Sensitivity, Specificity, AUC and NRI	NR	
				mGFR ≥60 ml/min/1.73m^2	Accuracy (P30) [95% CI]	93% [88-97]	
					Bias [95% CI]	4.3 [1.2 to 6.2]	
					Precision [95% CI])	RMSE: 11.1 [10.1-12.1] IQR:15.8 [13.0-18.7]	
				mGFR <60	Accuracy (P30) [95% CI]	76% [70-81]	
					Bias [95% CI]	0.6 [-0.7 to 2.3]	
					Precision [95% CI])	RMSE: 10.7 [9.5-11.8] IQR:11.7 [9.8-13.6]	
				CKD-EPI$_{cys}$ (cystatin C based equation)	Accuracy (P30) [95% CI]	86% [82-89]	
					Bias [95% CI]	-1.2 [-2.2 to 0]	
					Precision [95% CI]	RMSE:10.5[9.6-11.4] IQR:14.2 [12.5-15.9]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					Sensitivity, Specificity, AUC and NRI	NR	
				mGFR ≥60 ml/min/1.73m^2	Accuracy (P30) [95% CI]	91% [86-95]	
					Bias [95% CI]	3.4 [0.7 to 6.5]	
					Precision [95% CI])	RMSE: 12.2 [10.4-13.7] IQR: 14.4 [11.9-16.8]	
				mGFR <60	Accuracy (P30) [95% CI]	82% [77-87]	
					Bias [95% CI]	-2.9 [-3.7 to -1.9]	
					Precision [95% CI])	RMSE:9.2 [8.2-10.2] IQR:10.7 [8.1-13.2]	
				CKD-EPI$_{cr-cys}$ (creatinine and cystatin C based equation)	Accuracy (P30) [95% CI]	86% [82-90]	
					Bias [95% CI]	0.8 [-0.4 to +1.9]	
					Precision [95% CI]	RMSE:9.8 [9.0-10.5] IQR:12.7 [11.5-13.9]	
					Sensitivity, Specificity, AUC and NRI	NR	
				mGFR ≥60 ml/min/1.73m^2	Accuracy (P30) [95% CI]	94% [90-97]	
					Bias [95% CI]	4.8 [2.1 to 6.8]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					Precision [95% CI])	RMSE: 11.0 [9.8-12.1] IQR: 13.3 [9.6-17.1]	
				mGFR <60	Accuracy (P30) [95% CI]	81% [75-86]	
					Bias [95% CI]	-1.6 [-2.8 to -0.2]	
					Precision [95% CI])	RMSE: 8.9 [7.8-9.8] IQR: 10.3 [8.4-12.2]	

Table 22: KONG2013

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Kong et al 2013[350] **Country:** China	Prospective cohort enrolled from nine renal institutes of tertiary hospitals located in different geographic	Jaffe kinetic method calibrated using traceable high-level isotope dilution mass spectrometry reference Scr.	**Reference standard**: ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) plasma	MDRD $175 \times S_{Cr-}^{1.154} \times (age)^{-0.203} \times 0.742$ [if female]	Accuracy (P30) [95% CI]	69.8 (95% CI not reported)	Cohort included healthy volunteers. Chinese population only. 720 participants
					Bias [95% CI] (defined as the mean difference [eGFR-mGFR])	-5.49 [-6.57 to -4.23]	
					Precision [95% CI] (defined IQR [mGFR-eGFR])	23.4 (95% CI not reported)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	regions of China. 51% women, 3.8% diabetic nephropathy, Mean age (SD): 48 (16). Excluded people with AKI, RRT, severe oedema, skeletal muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure, ketoacidosis, or taking cimetidine. **Patients**, n: 977 (682 [70%] with CKD and 295 healthy		clearance. **Mean (SD) ml/min/1.73 m^2:** Total study population: 68.3 (37) People with CKD: 55.3 (35) Healthy volunteers: 98.4 (21)		Sensitivity, Specificity and Area under the curve (AUC)	NR	wit CKD underwent GFR measurement and 38 outliers were deleted.
					Net Reclassification Index (NRI)	NR	
				CKD-EPI (serum creatinine) (for white or other non-black): female and sCr ≤62µmol/L: 144 x $(sCr/ 62)^{-0.329}$ x 0.993^{age} ; female and sCr >62µmol/L: 144 x $(sCr/ 62)^{-1.209}$ x 0.993^{age} ; male and sCr ≤80µmol/L: 141 x $(sCr/ 80)^{-0.411}$ x 0.993^{age} ; and male and sCr	Accuracy (P30) [95% CI]	73.4 (95% CI not reported)	
					Bias [95% CI] (defined as the median difference [eGFR-mGFR])	-0.44 [-1.57 to -0.69]	
					Precision [95% CI]	20.5 (95% CI not reported)	
					Sensitivity (in predicting CKD stages 3-5) [95% CI]	87.9% (95% CI not reported)	
					Specificity (in predicting CKD stages 3-5) [95% CI]	91.6% (95% CI not reported)	
					Area under the curve (AUC) and Net Reclassification Index (NRI)	NR	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	volunteers) Subgroups: CKD Stage 1 n=125 CKD Stage 2 n=161 CKD Stage 3 n=197 CKD Stage 4 n=101 CKD Stage 5 n=98			CKD Stage 1	Accuracy (P30)	89.6	
					Bias [95% CI]	-15.7 [-18.4 to -13.0]	
					Precision [95% CI]	20.5	
					Sensitivity [95% CI]	60.0	
					Specificity [95% CI]	93.7	
				CKD Stage 2	Accuracy (P30)	84.5	
					Bias [95% CI]	2.0 [-6.0 to 4.5]	
					Precision [95% CI]	24.1	
					Sensitivity [95% CI]	63.4	
					Specificity [95% CI]	81.2	
				CKD Stage 3	Accuracy (P30)	68.0	
					Bias [95% CI]	6.5 [4.8 to 8.2]	
					Precision [95% CI]	15.1	
					Sensitivity [95% CI]	71.1	
					Specificity [95% CI]	86.6	
				CKD Stage 4	Accuracy (P30)	54.5	
					Bias [95% CI]	5.5 [3.8 to 7.3]	
					Precision [95% CI]	10.3	
					Sensitivity [95% CI]	51.5	
					Specificity [95% CI]	94.5	
				CKD Stage 5	Accuracy (P30)	49.0	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					Bias [95% CI]	3.0 [1.9 to 4.1]	
					Precision [95% CI]	6.7	
					Sensitivity [95% CI]	73.5	
					Specificity [95% CI]	98.1	

Table 23: KOPPE2013

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Koppe et al 2013[352] **Country:** France	People aged 70 years or older referred to a single centre for inulin clearance for suspected or established renal dysfunction. No exclusions mentioned in study. Mean age 75.3 (range 70-88.4) years; 43%	Creatinine assyas were carried out using an enzymatic method (Roche, France) with calibratiors defined by isotope dilutaion mass spectrometry in the same laboratory.	**Reference standard**: Inulin **Mean (SD) ml/min /1.73m^2:** 41.3 (range 10.0-88.9)	MDRD	Accuracy (P30) [95% CI]	70.7% [95% CI not reported]	All European ancestry so no analysis on other ethnicities. Also reports outcomes for age 70-75 years (n=128), 76-80 years (n=70) and >80 years
					Bias [95% CI] (defined as the median difference [eGFR-mGFR])	5.8 [95% CI not reported]	
					Precision [95% CI] (defined as RMSE of differences eGFR-mGFR)	RMSE: 14.9 [95% CI not reported]	
					Sensitivity, Specificity, AUC and NRI	NR	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	female; 22% diabetes. **Patients**, n: 224			CKD-EPI$_{cr}$ (creatinine based equation)	Accuracy (P30) [95% CI]	72.0% [95% CI not reported]	(n=26). Also reports outcomes for BIS-1 serum creatinine equation (not in protocol for this review)
					Bias [95% CI]	5.4 [95% CI not reported]	
					Precision [95% CI])	RMSE: 12.8 [95% CI not reported]	
					Sensitivity, Specificity, AUC and NRI	NR	

Table 24: LEVEY2009 (STEVENS2010)

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Levey et al 2009[379] Stevens et al 2010[652]	External validation data set from 16 studies. 45% women, 28%	Roche enzymatic method (Roche–Hitachi P-Module with Roche Creatininase Plus	**Reference standard**: ^{125}I-iothalamate (urine) and others	MDRD	Accuracy (P30) [95% CI]	80.6 [79.5-82.0]	Bias for CKD EPI differs between Levey and Stevens ?reason
					Bias* [95% CI] (defined as the median difference [eGFR-mGFR])	-5.5 [-5.9 to -5.0]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Country: USA	diabetic, 10% black, Mean age (SD): 50 (15). 16% kidney donors and 29% kidney transplant recipients **Patients**, n: 3896 Subgroups: GFR <60 n=1852 GFR ≥60 n=1473 Black n=384 White/other n=3512	assay) recalibrated to standardized SCr at the Cleveland Clinic.	**Mean (SD) ml/min/1.73 m^2:** 68 (36)		Precision [95% CI] (defined as as the root mean square error (RMSE) for the regression of estimated GFR on measured GFR) and IQR [mGFR-eGFR]	RMSE: 0.274 [0.265-0.283] IQR:18.3 [17.4-19.3]	Stevens et al also reports bias at different eGFR levels (including due to race at these levels). Cohort included kidney donors and kidney transplant recipients. *Bias reported as median difference [mGFR-eGFR]; median difference [eGFR-mGFR] calculated by NCGC.
					Sensitivity, Specificity Area under the curve (AUC)	NR	
					Net Reclassification Index (NRI)	NR	
				eGFR <60	Accuracy (P30)	77.2 [75.5-79.0]	
					Bias [95% CI]	-3.4 [-4.0 to -2.9]	
					Precision [95% CI]	RMSE: 0.294 [0.280-0.308] IQR: 12.9 [12.0-13.6]	
					Sensitivity [95% CI]	95%	
					Specificity [95% CI]	82%	
				eGFR ≥60	Accuracy (P30)	84.7 [83.0-86.3]	
					Bias [95% CI]	-10.6 [-11.3 to -9.8]	
					Precision [95% CI]	RMSE: 0.248 [0.238-0.258]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
						IQR: 25.7 [24.4-27.1]	
				Black	Bias [95% CI])	-0.3	
					No other outcomes reported for this subgroup.		
				White/ other	Bias [95% CI]	-6.0	
					No other outcomes reported for this subgroup.		
				CKD-EPI (serum creatinine)	Accuracy (P30) [95% CI]	84.1 [83.0-85.3]	
					Bias [95% CI] (defined as the median difference [eGFR-mGFR])	-2.5 [-2.9 to -2.1]	
					Precision [95% CI]	RMSE: 0.250 [0.241-0.259] IQR: 16.6 [15.9-17.3]	
					Sensitivity, Specificity Area under the curve (AUC)	NR	
					Net Reclassification Index (NRI)	NR	
				eGFR <60	Accuracy (P30)	79.9 [78.1-81.7]	
					Bias [95% CI]	-2.1 [-2.4 to -1.7]	
					Precision [95% CI]	RMSE: 0.284 [0.270-0.298] IQR: 11.3 [10.7-12.1]	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					Sensitivity [95% CI]	91%	
					Specificity [95% CI]	87%	
				eGFR ≥60	Accuracy (P30)	88.3 [86.9-89.7]	
					Bias (median percentage difference)	-3.5 [-4.5 to -2.6]	
					Precision [95% CI]	RMSE: 0.213 [0.203-0.233] IQR: 24.2 [22.8-25.3]	
				Black	Bias [95% CI]	1.1	
					No other outcomes reported for this subgroup		
				White/other	Bias [95% CI]	-2.5	
					No other outcomes reported for this subgroup		

Table 25: MICHELS2010

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Michels et al 2010[451] **Country**:	Potential kidney donors and adult patients who	Plasma creatinine measured with IDMS-validated	**Reference standard**: ^{125}I-iothalamate	Abbreviated MDRD 175 x $S_{Cr}^{-1.154}$ x (age)$^{-0.203}$ x 0.742 [if female] x 1.210 [if black]	Accuracy (P30) [95% CI]	81.2%	Plasma creatinine and GFR
					Bias [95% CI]	14.6ml/min	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
The Netherlands	underwent a GFR measurement for clinical reasons; measured GFR at least 15 ml/min. 56% female, mean (SD) age 44.3 (14.5); 12% black **Patients**, n: 271	enzymatic assay on automated analyser (Hitachi H911, Boehringer Mannheim, Mannheim, Germany).	**Mean (SD) ml/min/1.73 m²:** 72.6 (30.4) ml/min/1.73 m^2		(defined as the mean difference [eGFR-mGFR])		measurement no on the same day for most patients (but patients found to be stable); Small single centre study; 178 patients excluded because no height measurement.
					Precision [95% CI] (defined as SD of differences eGFR-mGFR)	19.9	
					Sensitivity, Specificity, AUC and NRI	NR 65% patients classified correctly	
				CKD-EPI female and sCr ≤0.7: $(sCr/0.7)^{-0.329} \times 0.993^{age} \times 144$ [if white or other] or x 166 [if black]; female and sCr >0.7: $(sCr/0.7)^{-1.209} \times 0.993^{age} \times 144$ [if white or other] or x 166 [if black]; male and sCr ≤0.9: $(sCr/0.9)^{-0.411} \times 0.993^{age} \times 141$ [if white or other] or x 163 [if black]; and male and sCr >0.9: $(sCr/0.9)^{-1.209} \times 0.993^{age} \times 141$ [if white or other] or x 163 [if black]	Accuracy (P30) [95% CI]	84.5%	
					Bias [95% CI]	12.3ml/min	
					Precision [95% CI]	12.1	
					Sensitivity, Specificity, AUC and NRI	NR 69% patients classified correctly	

Table 26: MURATA2011

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Murata et al 2011[462] **Country**: USA	All patients undergoing iothalamate clearance (clinical indications were potential kidney donor, post-nephrectomy kidney donor, native chronic kidney disease, kidney transplant recipient (n=1375), non-kidney organ transplant recipient; excluded <18 years; kidney assessment for chemotherapy dosing, paraplegic or	Creatinine measured using IDMS-traceable Roche enzymatic method.	**Reference standard**: Non-radiolabelled iothalamate clearance; concentrations measured using capillary electrophoresis on a Beckman MDQ analyser **Mean (SD) ml/min/1.73m^2 :** 55.9 (29.7) Mean for potential kidney donors subgroup: 99ml/min/1.73 m^2	MDRD (not further defined)	Accuracy (P30) [95% CI]	77.6%	Too few non-Caucasian people to assess effect of ethnicity. 1375/5238 (26%) kidney transplant recipients.
					Bias [95% CI] defined as difference in mean eGFR-mGFR	-4.1	
					Precision [95% CI]	NR	
					Sensitivity [95% CI] (threshold mGFR <60) n=10/583 (2%)	potential kidney donor (no known CKD) 70%	
					Specificity [95% CI] (threshold mGFR <60)	potential kidney donor (no known CKD) 94%	
					Sensitivity [95% CI] (threshold mGFR <80) n=97/583 (17%)	potential kidney donor (no known CKD) 89%	
					Specificity [95% CI] (threshold mGFR <80)	potential kidney donor (no known CKD) 48%	
					Area under the curve (AUC) and Net Reclassification Index (NRI)	NR	
				CKD-EPI (sCr, not	Accuracy (P30) [95% CI]	78.4%	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	quadriplegic, neurogenic bladder, dialysis patients, amputees. Mean (SD) age 56.1 (14.8); 89% Caucasian, 2% African-American **Patients**, n: 5238			further defined)	Bias [95% CI]	-0.7	
					Precision [95% CI]	NR	
					Sensitivity [95% CI] (threshold mGFR <60) n=10/583 (2%)	potential kidney donor (no known CKD) 50%	
					Specificity [95% CI] (threshold mGFR <60)	potential kidney donor (no known CKD) 98%	
					Sensitivity [95% CI] (threshold mGFR <80) n=97/583 (17%)	potential kidney donor (no known CKD) 71%	
					Specificity [95% CI] (threshold mGFR <80)	potential kidney donor (no known CKD) 76%	
					Area under the curve (AUC) and Net Reclassification Index (NRI)	NR	

Table 27: NYMAN2011

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Nyman et	External	Creatinine	**Reference**	MDRD 175 x (sCr/	Accuracy (P30) [95% CI]	79.9 [77.2 to 82.6]	95% CI not

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
al 2011[494] **Country**: Sweden	validation; consecutive patients referred for determination of GFR aged ≥18 years; patients on dialysis excluded; Median (2.5 and 97.5 percentiles) age 60(26-85); 44% female; 100% Caucasian **Patients**, n: 850 Subgroups: GFR 60-89 n=219 GFR 30-59 n=232 Age >80 n=64	measured using IDMS-traceable assay. (Roche enzymatic at Lund Hospital and Beckman modified Jaffe at Malmo Hospital)	**standard**: Iohexol clearance **Mean (SD) ml/min/1.73 m^2:** Median (2.5 and 97.5 percentiles) 55 (9-121))	88.4)$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female] x 1.210 [if African-American]	Bias [95% CI] (defined as the median difference [eGFR-mGFR] and median percentage difference)	1.2 [0.5 to 2.1] ml/min/1.73m^2 and -3.4% [1.3 to -5.5]	reported for subgroups. Bias and P30 also reported for GFR <15; 15-29; <30 and ≥90 and age 18-29, 30-39, 40-49, 50-59, 60-69, 70-79. P10 also reported overall and for all GFR subgroups.
					Precision [95% CI] (defined as IQR of differences eGFR-mGFR)	13.8 [12.4 to 14.9] ml/min/1.73m^2	
					Sensitivity, Specificity, Area under the curve (AUC)	NR	
					Net Reclassification Index (NRI)	Overall 66.9% patients classified correctly, performed best at 30-59 ml/min/1.73m^2 where 74% classified correctly	
				GFR 60-89ml/min/1.73m^2	Accuracy (P30)	87.2%	
					Bias	1.3 ml/min/1.73m^2 and 1.7%	
				GFR 30-59ml/min/1.73m^2	Accuracy (P30)	83.6%	
					Bias	2.4 ml/min/1.73m^2 and 4.9%	
				Age ≥ 80 years	Accuracy (P30)	71.9%	
					Bias (median	17.7%	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					percentage difference)		
				CKD-EPI (for white or other non-black): female and sCr ≤62µmol/L: 144 x $(sCr/ 62)^{-0.329}$ x 0.993^{age} ; female and sCr >62µmol/L: 144 x $(sCr/ 62)^{-1.209}$ x 0.993^{age} ; male and sCr ≤80µmol/L: 141 x $(sCr/ 80)^{-0.411}$ x 0.993^{age} ; and male and sCr >80µmol/L: 141 x $(sCr/ 80)^{-1.209}$ x 0.993^{age}	Accuracy (P30) [95% CI]	79.5 [76.8 to 82.2]	
					Bias [95% CI] (defined as the median difference [eGFR-mGFR] and median percentage difference)	2.3 [1.4 to 3.2] ml/min/1.73m^2 and 5.4% [3.9 to 7.9]	
					Precision [95% CI]	13.5 [12.1 to 14.8] ml/min/1.73m^2	
					Sensitivity, Specificity, AUC	NR	
					Net Reclassification Index (NRI)	Overall 67.8% patients classified correctly, performed best at >90ml/min/1.73m^2 where 78.5% classified correctly and <15 ml/min/1.73m^2 where 75.5% classified correctly.	
				GFR 60-89ml/min/1.73m^2	Accuracy (P30)	84.5%	
					Bias	6.5 ml/min/1.73m^2 and 8.6%	
				GFR 30-	Accuracy (P30)	75.0%	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				59ml/min/1.73m^2	Bias	4.2 ml/min/1.73m^2 and 9.3%	
				Age ≥ 80 years	Accuracy (P30)	82.8%	
					Bias (median percentage difference)	7.6%	

Table 28: SCHAEFFNER2012

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Schaeffner et al 2012[612] **Country**: Germany	Age 70 or older; German statutory health insurance; living in Berlin; excluded if receiving dialysis or kidney transplant. All white, mean age 78.5 years, 42.8% female, 21.4%	Serum creatinine measured using IDMS traceable enzymatic method; cystatin C measured by particle-enhanced nephelometric assay using BN Prospec analyser (Siemens	**Reference standard**: Iohexol clearance **Mean (SD) ml/min/1.73m^2 :** mean 60.3 (range 15.5-116.7)	MDRD: 175 x creat$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female]	Accuracy (P30) [95% CI]	70.9%	Note results for MDRD and CKD-EPI only reported for validation sample (n=285). Not random sample of participants; only white
					Bias [95% CI] (defined as the median difference [eGFR-mGFR])	11.29	
					Precision [95% CI] (defined as IQR of difference [eGFR-mGFR])	13.8	
					Sensitivity,	53.0% (calculated by NCGC)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	diabetes. **Patients**, n: N=285 in validation sample. Originally 610, 40 excluded (27 incomplete number of iohexol measurements, 12 insufficient fit of Schwartz model for iohexol measurements, 1 outlying mGFR of 300ml/min/1.73 m^2) so final number in total sample 570.	Healthcare Diagnostics, formerly Dade-Behring, Marburg, Germany) (traceable) and calibrated to international standard.			Specificity	98.0% (calculated by NCGC)	participants with mild to moderate reductions in kidney function so not necessarily generalisable to other ethnicities or to patients with more severe kidney dysfunction. BIS 2 excluded as not externally validated equation.
					AUC	NR	
					NRI	Overall 66 patients (23.2%) misclassified, 3 (2.0%) wrongly considered <60ml/min and 63 (47%) ≥60ml/min	
				CKD-EPI female and sCr ≤62µmol/L: 144 x $(sCr/ 0.7)^{-0.329}$ x 0.993^{age} ; female and sCr >62µmol/L: 144 x $(sCr/ 0.7)^{-1.209}$ x 0.993^{age} ; male and sCr ≤80µmol/L: 141 x $(sCr/ 0.9)^{-0.411}$ x 0.993^{age} ; and male and sCr >80µmol/L: 141 x $(sCr/ 0.9)^{-1.209}$ x 0.993^{age} ; all ml/min/1.73m^2	Accuracy (P30) [95% CI]	77.9%	
					Bias [95% CI]	9.69	
					Precision [95% CI]	13.0	
					Sensitivity	59.7% (calculated by NCGC)	
					Specificity	97.4% (calculated by NCGC)	
					AUC	NR	
					NRI	Overall 58 patients (20.4%) misclassified, 4 (2.6%) wrongly considered <60ml/min and 54 (40.3%)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
						≥60ml/min	
				CKD EPI Cystatin C (CysC1): 76.7 x cystatin $C^{-1.19}$	Accuracy (P30) [95% CI]	NR	
					Bias [95% CI]	8.71	
					Precision [95% CI], Sensitivity, Specificity, AUC, NRI	NR	
				CKD EPI cystatin C (CysC2): 127.7 x cystatin $C^{-1.17}$ x $age^{-0.13}$ x 0.91 [if female]	Accuracy (P30) [95% CI]	89.1%	
					Bias [95% CI]	1.92	
					Precision [95% CI]	11.8	
					Sensitivity	79.1% (calculated by NCGC)	
					Specificity	90.0% (calculated by NCGC)	
					AUC	NR	
					NRI	Overall 43 patients (15.1%) misclassified, 15 (9.9%) wrongly considered <60ml/min and 28 (20.9%) ≥60ml/min	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				CKD EPI combined sCr and Cystatin C: 177.6 x $creat^{-0.65}$ x cystatin $C^{-0.57}$ x $age^{-0.20}$ x 0.82 [if female]	Accuracy (P30) [95% CI]	81.4%	
					Bias [95% CI]	7.66	
					Precision [95% CI]	11.0	
					Sensitivity	59.7% (calculated)	
					Specificity	97.4% (calculated)	
					AUC	NR	
					NRI	Overall 58 patients (20.4%) misclassified, 4 (2.6%) wrongly considered <60ml/min and 54 (40.3%) ≥60ml/min	

Table 29: STEVENS2008

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Stevens et	Participants	Serum creatinine	**Reference**	MDRD standardised	Accuracy (P30) [95% CI]	85% (84-86)	New equations

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
al 2008[651] **Country**: USA, France	screened for 3 chronic kidney disease studies in the USA (MDRD, African American Study of Kidney disease and hypertension [AASK], Captopril trial by the Collaborative Study Group [CSG]) and a clinical population in Paris, France. Total sample: Mean (SD) age 52 (13); 37% female; 53% black; 43% white; 4% other; 13% diabetes.	recalibrated to standardized SCr at the Cleveland Clinic.	**standard**: ^{125}iothalamate in the USA studies and ^{51}Cr-EDTA in the France stud **Mean (SD) ml/min/1.73 m^2:** 48 (25)	to IDMS: 175 x creat$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female] x 1.212 [if black]	Bias* [95% CI] (defined as the median difference [eGFR-mGFR] and median percentage difference)	-2 (-3 to -2) ml/min/1.73m^2 ; 8 (6 to 11)%	developed using 2/3 data from USA; internal validation using remaining 1/3 USA data; external validation using Paris, France study. Study population composed mainly of patients with CKD. Racial subgroup analysis used whole data set i.e. not external validation. Only 1 external validation set used so results may not be generalisable to other
					Precision [95% CI] (defined as RMSE [log scale] and IQR of differences eGFR-mGFR)	RMSE (95% CI) 0.231 (0.213 to 0.249) IQR (95% CI) 8 (7 to 9) ml/min/1.73m^2 ; 24 (22-27)%	
					Sensitivity, Specificity, AUC and NRI	NR	
				CKD-EPI (serum creatinine) female and sCr ≤0.7: (sCr/0.7)$^{-0.329}$ x 0.993^{age} x 144 [if white or other] or x 166 [if black]; female and sCr >0.7: (sCr/0.7)$^{-1.209}$ x 0.993^{age} x 144 [if white or other] or x	Accuracy (P30) [95% CI]	84% (83-85)	
					Bias [95% CI]	-2 (-3 to -1)ml/min/1.73m^2 and 7 (4-9)%	
					Precision [95% CI]	RMSE (95% CI) 0.229 (0.210 to 0.247) IQR (95% CI) 8 (7 to 9) ml/min/1.73m^2 ; 25 (22-29)%	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	External validation: Mean (SD) age 59 (15); 29% female; 8% black; 79% white; 13% other; 22% diabetes. **Patients**, n: Total sample n=3418 External validation n= 438 Internal validation n=1045 Derivation n= 2980			166 [if black]; male and sCr ≤0.9: $(sCr/0.9)^{-0.411}$ x 0.993^{age} x 141 [if white or other] or x 163 [if black]; and male and sCr >0.9: (sCr/ 0.9)-1.209 x 0.993age x 141 [if white or other] or x 163 [if black]	Sensitivity, Specificity, AUC and NRI	NR	populations. Cystatin C not standardised therefore not included in review. *Bias reported as median difference [mGFR-eGFR]; median difference [eGFR-mGFR] calculated by NCGC.
				White/ other	Accuracy (P30) [95% CI]	85%	
					Bias [95% CI]	0 (-0.3 to +0.3) ml/min/1.73m^2 ; 0.1 (-0.9 to +1.0)%	
					Precision [95% CI]	RMSE 0.220 IQR 8.2 ml/min/1.73m^2 ; 26.1%	
				African-American	Accuracy (P30) [95% CI]	84%	
					Bias [95% CI]	0.1 (-0.3 to +0.7) ml/min/1.73m^2 ; 0.4 (-0.8 to +1.3)	
					Precision [95% CI]	RMSE log scale 0.232	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
						IQR 13.7 ml/min/1.73m^2 ; 27.6%	

Table 30: TEO 2011 (and TEO2012)

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
Teo et al 2011[669] and Teo et al 2012[670] **Country**: Singapore	Patients with stable CKD (<20% difference in creatinine >60 days apart); >21 years; serum creatinine level with eGFR or mGFR 10-90ml/min; excluded if unable to consent, physical condition making phlebotomy difficult, unable	Serum creatinine measured using enzymatic method (creatininase) on the Siemens Advia 2400, calibrated to traceable IDMS. Cystatin C measured by particle-enhanced immunonephelo	**Reference standard**: ^{99m}Tc-DTPA **Mean (SD) ml/min/1.73m^2 :** 51.7 (27.5)	IDMS traceable MDRD: 175 x $sCr^{-1.154}$ x $age^{-0.203}$ x 0.742 [if female]	Accuracy (P30) [95% CI]	79.7% (74.6-84.9)	Study population only patients with CKD, excluded kidney transplant patients and healthy individuals. Small single centre study. Also reports 1 cystatin C and 2 combined sCr
					Bias [95% CI] (defined as the median difference [eGFR-mGFR])	-3.0 (-4.2 to -1.7)	
					Precision [95% CI] (defined as RMSE and IQR)	RMSE: 15.2 (12.1-18.3) IQR: 12.2 (10.0-14.4)	
					Sensitivity,	90.5%	
					Specificity	78.4%	
					AUC and NRI	NR	
				eGFR <60	Accuracy (P30) [95% CI]	78.8% (72.4-85.1)	
					Bias [95% CI]	-2.4 (-3.7 to -1.1)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	to collect urine samples successfully, acute kidney function deterioration, amputation, oedema, pleural effusion, ascites, skeletal muscle atrophy, condition interfering with GFR measurement. Mean (SD) age 58.4 (12.8); 48% female; 40.5% Chinese; 32% Malay; 27.5% Indian/ other **Patients**, n: 232	metry on a BN Prospec platform (Dade Behring).			Precision [95% CI]	RMSE: 12.6 (8.5-16.6) IQR: 9.2 (7.0-11.4)	and cystatin C equations with Chinese coefficients. Also reports outcomes for Malay and Indian/other subgroups
				eGFR >60	Accuracy (P30) [95% CI]	81.9% (73.1-90.8)	
					Bias [95% CI]	-5.3 (-9.5 to -1.2)	
					Precision [95% CI]	RMSE: 19.8 (14.9-24.8) IQR: 18.3 (10.3-26.4)	
				CKD-EPI: 141 x $\min(Scr/\kappa, 1)^{\alpha}$ x $\max(Scr/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] ml/min/1.73m^2 where κ=0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, "min" indicates the minimum of Scr/κ or 1 and "max" is the maximum of Scr/κ or 1.	Accuracy (P30) [95% CI]	82.8 (77.9-87.6)	
					Bias [95% CI]	-1.2 (-2.7 to +0.3) Chinese: -2.2 (-4.0 to -0.5)	
					Precision [95% CI]	RMSE: 13.8 (11.3-16.4) IQR: 12.1 (9.0-15.1) Chinese: RMSE: 13.1 (9.3-16.9); IQR 13.0 (8.4-17.6)	
					Sensitivity	88.6%	
					Specificity	85.1%	
					AUC and NRI	NR	
				eGFR <60	Accuracy (P30) [95% CI]	78.8% (72.4-85.1)	
					Bias [95% CI]	-1.5 (-2.8 to -0.1)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
	Subgroups: eGFR <60: n=160 eGFR >60: n=72 Chinese: n=94				Precision [95% CI]	RMSE: 12.9 (9.6-16.10 IQR: 9.3 (7.0-11.6)	
				eGFR >60	Accuracy (P30) [95% CI]	91.7% (85.3-98.1)	
					Bias [95% CI]	0.9 (-4.1 to 5.9)	
					Precision [95% CI]	RMSE: 15.8 (11.8- 19.8) IQR: 22.0 (16.7-27.2)	
				CKD EPI cystatin C (eGFR1): 76.7 x (-0.105 + 1.13 x cystatin C)$^{-1.19}$ ml/min/1.73m^2	Accuracy (P30) [95% CI]	86.6% (82.2-91.1) Chinese: 90.4 (84.6-96.3)	
					Bias [95% CI]	-0.4 (-2.3 to +1.4) Chinese:-1.3 (-3.3 to +0.7)	
					Precision [95% CI]	RMSE: 15.2 (11.6-18.7) IQR: 11.8 (9.7-13.8) Chinese: RMSE: 16.3 (10.5-22.2); IQR: 11.7 (7.6-15.8))	
					Sensitivity, Specificity, AUC and NRI	NR	
				CKD EPI cystatin C (eGFR2): 127.7 x (-0.105 + 1.13 x	Accuracy (P30) [95% CI]	87.1% (82.8-91.4) Chinese: 92.6 (87.1-98.0)	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
				cystatin C)$^{-1.17}$ x age$^{-0.13}$ x 0.91 [if female] x 1.06 [if black] ml/min/1.73m^2			
					Bias [95% CI]	-2.7 (-3.9 to -1.6) Chinese: -3.3 (-4.9 to -1.7)	
					Precision [95% CI]	RMSE: 14.3 (11.1-17.5) IQR: 10.6 (8.6-12.6) Chinese: RMSE: 14.6 (9.4-19.7); IQR: 11.2 (8.2-14.2)	
					Sensitivity, Specificity, AUC and NRI	NR	
				CKD EPI combined serum creatinine and cystatin C: 177.6 x sCr$^{-0.65}$ x (-0.105 + 1.13 x cystatin C)$^{-0.57}$ x age$^{-0.20}$ x 0.82 [if female] x 1.11 [if black] ml/min/1.73m^2	Accuracy (P30) [95% CI]	88.4% (84.2-92.6) Chinese: 88.3 (81.8-94.8)	
					Bias [95% CI]	-1.6 (-2.7 to -0.4) Chinese: -2.5 (-4.1 to -0.8)	
					Precision [95% CI]	RMSE: 13.6 (10.7-16.5) IQR: 10.5 (8.1-12.8) Chinese: RMSE: 13.8 (8.8-18.8)); IQR: 9.0 (6.2-11.8)	
					Sensitivity, Specificity,	NR	

Study and Country	Population	Serum creatinine (SCr)/ Cystatin C calibration and assay detail	Measured GFR	GFR estimation equation and subgroups	Outcomes		Limitations/ Comments
					Outcome measure	Effect size	
					AUC and NRI		

G.2 Markers of kidney damage

Table 31: Peralta 2011

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect size	Comments
Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to	Prospective cohort Country: USA	N= 26 643, USA (REGARDS) Reasons for Geographic and Racial Differences in Stroke Inclusion criteria: black and white participants ≥ 45 yrs,	See table below	ACR alone n=2485 Cystatin C alone n=963 ACR+ Cystatin C n=415 Creatinine alone n=701 Creatinine + ACR n=148 Creatinine + Cystatin C n=1172 All measures n=883 Covariates: Mortality associated with cystatin C, estimated glomerular filtration rate, and albuminuria Estimated GFR creatinine ≥ 60	See table below		Source of funding: National Institute of Neurological disorders and Stroke, National Institute of Health, Dept of Health and Human Services. Amgen Corp Blood was collected from participants during an in-home examination after a 12 hr fast. Serum creatinine was measured and calibrated to isotope dilution mass spectrometry

end-stage renal disease and mortality. JAMA. 2011; 305(15):1545-1552. *(Guideline Ref ID PERALTA2011)*		free of cancer and, at the time of the initial telephone call were able to answer the questions and were not living in an assisted living home. <u>Exclusion criteria:</u> Participants who were missing baseline data for serum creatinine, cystatin C, or urine albumin and creatinine. Those receiving dialysis or had received a renal transplant at study entry.		ml/min/1.73m^2 (i) Adjusts for age, race, income and educational attainment (ii) Adjusts for the above plus hypertension, diabetes, prevalent cardiovascular disease, smoking status and BMI Risk of death and end-stage renal disease associated with CKD stage 3 estimated by eGFR using creatinine and cystatin c (stage 3 defined as eGFR < 60 ml/min/1.73^2) using CKD-EPI equations. All-cause mortality over 4.6 yr (i) Mortality model adjusts for age, race, sex, income, education attainment, hypertension and diabetes (ii) As above plus hypertension, diabetes, prevalent cardiovascular disease, smoking status, BMI, waist circumference and log albumin-to-creatinine ratio End-stage renal disease over 4.6 yr (i) Model adjusts for age, race, sex, hypertension and diabetes (ii) As above plus log albumin-to-creatinine ratio		traceable methods. Cystatin C was measured by particle-enhanced immunonephelometry. Urine albumin was measured by nephelometry, and urine creatinine by the Jaffe method using the modular-P chemistry analyser.

		Length of follow up: Maximum 7 yrs 4 mths				

Table 32: Effect sizes: Peralta 2011

Mortality : Estimated GFR creatinine ≥ 60 ml/min/1.73m^2				
CKD defined by biomarkers	**Total no. of patients**	**Total no. of deaths**	**Adjusted model 1* HR (95%CI)**	**Adjusted model 2****
No CKD all	19 876	863	1 (reference)	1 (reference)
ACR alone	2485	241	1.9 (1.6 to 2.2)	1.7 (1.4 to 1.9)
Cystatin C alone	963	173	2.5 (2.1 to 3.0)	2.2 (1.9 to 2.7)
ACR + Cystatin	415	106	3.9 (3.1 to 4.7)	3.0 (2.4 to 3.7)
* Adjusts for age, race, income and educational attainment ** Adjusts for the above plus hypertension, diabetes, prevalent cardiovascular disease, smoking status and BMI				
Mortality : Estimated GFR creatinine < 60 ml/min/1.73m^2				
CKD defined by biomarkers	**Total no. of patients**	**Total no. of deaths**	**Adjusted model 1* HR (95%CI)**	**Adjusted model 2****
Creatinine alone	701	32	1 (reference)	1 (reference)
Creatinine + ACR	148	27	3.7 (2.2 to 6.2)	3.3 (2.0 to 5.6)
Creatinine + Cystatin C	1172	223	3.5 (2.4 to 5.1)	3.2 (2.2 to 4.7)
All biomarkers	883	276	6.6 (4.6 to 9.6)	5.6 (3.9 to 8.2)
* Adjusts for age, race, income and educational attainment ** Adjusts for the above plus hypertension, diabetes, prevalent cardiovascular disease, smoking status and BMI				

Risk of death and end-stage renal disease associated with CKD stage 3 estimated by eGFR using creatinine and cystatin c (stage 3 defined as eGFR < 60 ml/min/1.732) **All-cause mortality over 4.6 yr**					
Biomarker measures, estimated GFR ml/min/1.73^2	**No. of participants**	**No. of events**	**Rates per 1000 person-years**	**Adjusted model***	**Adjusted model****
Creatinine + Cystatin C ≥ 60	22 361	1104	10.9 (10.9 to 11.0)	1 (reference)	1 (reference)

Creatinine alone < 60	849	59	15.4 (14.9 to 15.9)	1.0 (0.7 to 1.2)	0.9 (0.7 to 1.1)
Cystatin C alone < 60	1378	278	47.0 (45.8 to 48.2)	2.6 (2.2 to 2.9)	2.1 (1.9 to 2.5)
Creatinine + cystatin C < 60	2055	799	57.8 (56.6 to 59.1)	2.8 (2.5 to 3.1)	2.1 (1.9 to 2.4)
* Mortality model adjusts for age, race, sex, income, education attainment, hypertension and diabetes ** As above plus hypertension, diabetes, prevalent cardiovascular disease, smoking status, BMI, waist circumference and log albumin-to-creatinine ratio					
Risk of death and end-stage renal disease associated with CKD stage 3 estimated by eGFR using creatinine and cystatin c (stage 3 defined as eGFR < 60 ml/min/1.732) **End-stage renal disease over 4.6 yr**					
Biomarker measures, estimated GFR ml/min/1.73^2	**No. of participants**	**No. of events**	**Rates per 1000 person-years**	**Adjusted model***	**Adjusted model****
Creatinine + Cystatin C ≥ 60	22 361	17	0.2 (0.1 to 0.3)	1 (reference)	1 (reference)
Creatinine alone < 60	849	2	0.5 (0.1 to 2.2)	3.9 (0.9 to 16.9)	2.5 (0.6 to 10.9)
Cystatin C alone < 60	1378	14	2.2 (1.3 to 3.8)	12.6 (6.2 to 25.9)	5.8 (2.8 to 12.1)
Creatinine + cystatin C < 60	2055	144	15.8 (13.5 to 18.6)	90.5 (53.2 to 153.9)	26.1 (14.9 to 45.7)
* Model adjusts for age, race, sex, hypertension and diabetes ** As above plus log albumin-to-creatinine ratio					

Table 33: Peralta 2011 Baseline characteristics

	No CKD (n=19 876)	ACR alone (n=2485)	Cystatin C alone (n=963)	ACR + cystatin C (n=415)	Creatinine alone (n=701)	Creatinine + ACR n=148	Creatinine + Cystatin C n=1172	All measures N=1172
Estimated GFR,								

	No CKD (n=19 876)	ACR alone (n=2485)	Cystatin C alone (n=963)	ACR + cystatin C (n=415)	Creatinine alone (n=701)	Creatinine + ACR n=148	Creatinine + Cystatin C n=1172	All measures N=1172
normal ≥ 60 ml/min/1.73^2 Creatinine Cystatin	 Normal Normal	 Normal Normal	 Normal Abnormal	 Normal Abnormal	 Abnormal Normal	 Abnormal Normal	 Abnormal Abnormal	 Abnormal Abnormal
ACR, normal: < 30 mg/g	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Age, mean (SD) y	63 (9)	65 (9)	70 (9)	69 (10)	71 (8)	79 (53)	74 (9)	71 (9)
Women %	55	52	50	43	62	53	57	46
Black %	38	52	34	46	39	55	34	50
Diabetes %	16	24	26	49	20	32	31	50
Hypertension %	52	38	73	82	71	82	83	87
Prevalent CVD %	17	73	33	44	27	32	41	47
Estimated GFR, median (IQR), ml/min/1.73^2 Cystatin C Creatinine	 92 (27) 91 (20)	 87 (29) 91 (23)	 55 (7) 71 (15)	 54 (9) 71 (16)	 70 (14) 55 (7)	 67.7 (9) 55 (7)	 48 (14) 49 (14)	 41 (18) 43 (19)

Table 34: Peralta 2011B

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
Peralta 2011B	Prospective cohort Country: USA	N = 11909 (6749 from MESA and 5160 from CHS) Inclusion criteria: participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS) MESA - recruited men and women (45-84 yearrs) free of cardiovascular disease, and who self-identified as	Mean age: MESA: All: 62 GFR not decreased: 61 (10) Decreased GFRcreat + GFRcys:73 (8) CHS: All 72 ± 5 years GFR not decreased: 72 (5) Decreased GFRcreat + GFRcys:76 (7) M:F: MESA: GFR not decreased: 2738 (48%) men Decreased GFRcreat + GFRcys:132 (49%) men CHS: GFR not decreased: 1322 (38%) men Decreased GFRcreat +	Markers: This study compares CKD classification by the estimated GFR values of creatinine (eGFRcreat) and cystatin C (eGFRcys) in ambulatory adults. All of the assays were performed in frozen serum specimens that were stored at -70°C. Cystatin C was measured by particle enhanced immunonephelometric assay with a nephelometer. Serum cystatin C was calibrated to Cleveland Clinic using internal standards supplied by the manufacturer to both sites. Serum creatinine was measured by a colorimetric method in	MESA (n) GFR not decreased Decreased GFRcreat only Decreased GFRcyc only Decreased GFR both CHS (n) GFR not decreased Decreased GFRcreat only Decreased GFRcyc only Decreased GFR both All-cause mortality -MESA n Decreased GFR_{creat} + GFR_{cys} (adjusted HR (95% CI)) All-cause mortality -CHS n Decreased GFR_{creat} + GFR_{cys} (adjusted HR (95% CI)) Cardiovascular disease (MI, cardiac arrest, stroke or cardiovascular death) -MESA n Decreased GFR_{creat} + GFR_{cys}	 5759 614 107 269 3639 605 227 689 223 1.93 (1.27, 2.92) 3345 1.74 (1.58, 1.93) 212 1.67 (1.06, 2.63)	Source of funding: Supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute for MESA. Supported by contract numbers N01-HC-85079 through

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
		white, African American, Hispanic, or Chinese American. Between July CHS: longitudinal study designed community-dwelling adults (≥ 65 yrs) Exclusion criteria: MESA: If they had physician diagnosed heart attack, angina, heart failure, stroke, transient ischemic attack, or atrial fibrillation; had undergone coronary artery bypass grafting,	GFRcys:335 (49%) men Ethnicity: MESA: All = 39% white, 28% black, 12% Chinese, and 22% Hispanic Decreased GFRcreat + GFRcys: 40% white, 13% black, 28% Chinese, and 20% Hispanic CHS: All = white (84%) and 16% black. Decreased GFRcreat + GFRcys: white (84%) and 16% black. CHS = Prevalent cardiovascular disease was present in 24% MESA = no prevalent cardiovascular disease at baseline Hypertension: MESA. Decreased	CHS. In MESA, serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center. Serum creatinine was calibrated directly to Cleveland Clinic in MESA and indirectly in CHS. Estimated the GFR using CKD-EPI creatinine equation and the CKD-EPI cystatin C equation without demographic coefficients: eGFRcys = 76.7 x cystatin $C^{-1.19}$. Both formulae were developed from the pooling of several cohorts with GFR	(adjusted HR (95% CI))		N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133; grant number U01 HL080295 from the National Heart, Lung, and Blood Institute; with additional contributions from the National Institute of Neurologic Disorders and Stroke.
					Cardiovascular disease - CHS n Decreased GFR_{creat} + GFR_{cys} (adjusted HR (95% CI))	2249 1.46 (1.29, 1.65)	
					Heart failure - CHS (MESA N/R) n Decreased GFR_{creat} + GFR_{cys} (adjusted HR (95% CI))	1407 1.43 (1.22, 1.67)	
					Kidney failure - CHS (MESA N/R) n Decreased GFR_{creat} + GFR_{cys} (adjusted HR (95% CI))	84 23.82 (12.68, 44.76)	
					All-cause mortality - CHS (MESA N/R) n (events/n) eGFRcys ≥60 and alb/cr <30 (adjusted HR (95% CI)) n (events/n) eGFRcys ≥60 and alb/cr >30 (adjusted HR (95% CI))	71/170 1.00 (ref) 181/200 3.41 (2.54, 4.59)	

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
		angioplasty, valve replacement, or pacemaker; or weighed >300 lbs. CHS: Excluded if they were not expected to remain in the current community for 3 yrs or longer, were receiving treatment for cancer, or were unable to provide informed consent. The initial 5201 participants were enrolled from Jan 1989 to June 1990; an additional 687 black participants	GFRcreat + GFRcys: 80% CHS. Decreased GFRcreat + GFRcys: 66% <u>Diabetes:</u> MESA. Decreased GFRcreat + GFRcys: 26% CHS. Decreased GFRcreat + GFRcys: 20% <u>CKD:</u> In MESA, 9% had CKD by the creatinine-based equation only, 2% had CKD by the cystatin C-based equation only, and 4% had CKD by both equations; in CHS, these percentages were 12, 4, and 13%, respectively.	measured from iothalamate clearance. Urine albumin and creatinine were not available at baseline in CHS but were measured at year 7 in CHS using nephelometry. Decreased GFR refers to eGFR<60ml/min/ $1.73m^2$ <u>Statistical analysis:</u> Estimated the incidence rates of death and cardiovascular disease in MESA and CHS, and the rates of heart failure and kidney failure in CHS only. Using Cox proportional hazard models, they determined their association with the risks for death, cardiovascular events, incident heart failure,	(Adjusted for age, gender, race, diabetes, smoking, total cholesterol, body mass index, prevalent CVD, and C-reactive protein)		This work was also funded by the NIDDK <u>Other outcomes:</u> Limitations:

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
		were recruited and enrolled by June 1993. Follow up: MESA: mean 4.7 years CHS: 12.2 years		and kidney failure in separate models. Adjusted for covariates chosen a priori (listed below) as potential confounders of the association of eGFR <60 ml/min/1.73m^2 with adverse outcomes. Covariates: Adjusted for age, race, gender, diabetes, hypertension, LDL, HDL, CRP, and prevalent CVD for CHS (persons with baseline CVD were excluded for incident CVD analyses). Reference group is GFR not decreased.			

Table 35: Waheed 2012

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
Waheed	Prospecti	N = 9489	Mean age: 63 yrs	Markers:	Mortality	Adjusted Hazard	Source of

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
2012	ve cohort Country: USA	Subgroups: No CKD: n=7950 eGFRcreatinine only: n=219 ACR only: n=476 eGFR cystatin only: n= 476 eGFRcreatine and eGFRcystatin: n=185 eGFRcreatinine and ACR: n=24 eGFR cystatin and ACR: n=63 All 3 markers abnomal: n=96 Inclusion criteria: ARIC study of 15,792 participants, aged 45-64 years, recruited from 1987-	**a)** $eGFR_{creatinine}$.+ $eGFR_{cystatin.}$:67.5 (4.7) **b)** $eGFR_{creatinine}$ + ACR: 65.6 (5.5) **c)** $eGFR_{cystatin}$.+ ACR: 66.1 (5.3) **d)** All 3 markers: 66.8 (5.2) M:F: 58% female **a)** 63.2% **b)** 54.2 **c)** 47.6 **d)** 54.2 Ethnicity: 22% African American White: **a)** 84.3% **b)** 54.2% **c)** 76.2% **d)** 66.7% Hypertension: 45% **a)** 74.1% **b)** 70.8%	**1.** $eGFR_{creatinine}$. Serum creatinine concentration was measured using a modified kinetic Jaffe method. The CKD-EPI creatinine equation was used to estimate $eGFR_{creatinine}$ **2.** $eGFR_{cystatin.}$ Plasma cystatin C concentration was measured byparticle-enhanced immunonephelometric assay from frozen stored samples. $eGFR_{cystatin}$ calculated using CKD-EPI cycstatin C equation. **3.** Urinary albumin:creatinine ratio (ACR). Calculated from a random urine sample from urine albumin and urine creatinine concentrations. Jaffe method used to	$eGFR_{creatinine}$.+ $eGFR_{cystatin.}$ $eGFR_{creatinine}$ + ACR $eGFR_{cystatin}$.+ ACR All 3 markers	ratios (95% CI) 1.86 (1.42, 2.44) 1.26 (0.52, 3.05) 2.47 (1.70, 3.61) 3.69 (2.79, 4.87)	funding: The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and blood Institute contracts. Siemens Healthcare Diagnostics provided the reagents and loan of BNII instrument to conduct the cystatin C assays. Other outcomes: Further
					Coronary heart disease (a hospitalised definite or probable MI, fatal CHD or a coronary revascularization procedure). $eGFR_{creatinine}$.+ $eGFR_{cystatin.}$ $eGFR_{creatinine}$ + ACR $eGFR_{cystatin}$.+ ACR All 3 markers	Adjusted Hazard ratios (95% CI) 1.85 (1.35, 2.5) 1.03 (0.38, 2.76) 0.93 (0.49, 1.74) 3.01 (2.15, 4.20)	
					Heart failure (Codes ICD9:428 and ICD10: I50) $eGFR_{creatinine}$.+ $eGFR_{cystatin.}$ $eGFR_{creatinine}$ + ACR $eGFR_{cystatin}$.+ ACR All 3 markers	Adjusted Hazard ratios (95% CI) 2.00 (1.44, 2.80) 4.31 (2.28, 8.13) 3.25 (2.10, 5.03) 6.92 (5.14, 9.31)	
					AKI (validated AKI events from hospital discharge diagnosis [ICD9: 584.5-584.9, ICD10: N17.0-N17.9]. Also those with AKI on their death certificate.)	Adjusted Hazard ratios (95% CI)	

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
		1989. Exclusion criteria: Those with race other than African American and white (n = 31), those with missing data (n = 1302), and those with prevalent cardiovascular disease at baseline (n = 834) Follow up: Followed by annual telephone calls (response rate >90%) and 4 standardized examinations (n = 11,656) each approximately 3	**c)** 81.0 **d)** 89.6% Diabetes: 15% **a)** 20% **b)** 50% **c)** 43.6% **d)** 39.6% CKD: 16.2% had CKD by any marker.	measure urine creatinine, whereas urine albumin was measured using the nephelometric method. Statistical analysis: Divided cohort into: • No CKD by any marker ($eGFR_{creatinine}$.≥60 and $eGFR_{cystatin}$.≥60 and ACR <30 [reference]) n = 7950 • $eGFR_{creatinine}$.+ $eGFR_{cystatin.}$ (Both.<60ml/min/1.73 m^2) n = 185 • $eGFR_{creatinine}$ + ACR ($eGFR_{creatinine}$.<60ml/min/1.73m^2 and ACR ≥30 mg/g) n = 24 • $eGFR_{cystatin}$.+ ACR ($eGFR_{cystatin}$.<60ml/min/1.73m^2 and ACR ≥30 mg/g) n = 63 • All 3. n = 96	$eGFR_{creatinine}$ + $eGFR_{cystatin.}$ $eGFR_{creatinine}$ + ACR $eGFR_{cystatin}$.+ ACR All 3 markers ESRD (ICD9 or ICD10 codes for kidney transplant, dialysis, or procedural codes indicating dialysis. Also those with an earlier diagnosis of CKD who had an underlying cause of death being ARF on their death certificate) $eGFR_{creatinine}$.+ $eGFR_{cystatin.}$ $eGFR_{creatinine}$ + ACR $eGFR_{cystatin}$.+ ACR All 3 markers	3.90 (2.65, 5.74) 2.19 (0.70, 6.9) 3.96 (2.18, 7.18) 9.78 (6.63, 14.43) Adjusted Hazard ratios (95% CI) 14.57 (6.75, 31.46) 8.91 (2.06, 38.49) 14.55 (5.38, 39.32) 125.98 (73.06, 217.22)	baseline characteristic (cholesterol, BMI, smokers and individual marker levels) Single comparison of markers (hazard ratios). Limitations:

Reference	Study type	Number of patients	Patient characteristics	Markers and Covariates	Prognostic factors	Effect sizes	Comments
		years apart. Median follow up of 11.2 years		Covariates: All hazard ratios adjusted for age, race, sex, and total cholesterol, history of diabetes, hypertension, smoking, BMI, and C-reactive protein eGFR, estimated GFR			

G.3 Classification

Table 36: ASTOR2011C

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Brad C. Astor, Kunihiro Matsushita, Ron T. Gansevoort, Marije van der Velde, Mark Woodward, Andrew S. Levey, Paul E de Jong, Josef Coresh, Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 79 (12):1331-1340, 2011. (Guideline ref ID ASTOR2011C)	21,688 participants 14 studies (6 RCTs, 4 observational studies of referred patients and 4 studies of participants identified by laboratory testing). **Cohorts with ACR:** British Columbia (Levin et al. 2008) CRIB (Landray et al. 2001) Grampian-ACR (Clark et al. 2007) MASTERPLAN	**Study type:** IPD meta-analysis **Inclusion:** Studies had to include primarily participants selected because of CKD, have information about baseline eGFR and urinary albumin or urinary protein excretion, and at least 50 cases of end stage renal disease (ESRD) or deaths. **Exclusion:** Individuals with ESRD. Data from transplant patients was not used in this	MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. Each study group asked to standardize serum creatinine measurements to isotope dilution mass spectrometry-traceable methods, but calibration was not uniform. Albuminuria was assessed as the urinary ACR or PCR, preferably measured in a first morning void urine sample. Spot urine samples or samples from 24-hour urine collections were used if first morning not available. If no quantitative albuminuria measurements available, data on dipstick proteinuria were collected. History of cardiovascular	**ESRD** was defined as the start of renal replacement therapy or death due to decreased kidney function and not due to acute kidney injury. HR (95% CI)	**ACR (mg/g)** ACR 30-299: 2.87 (1.91, 4.34) ACR 300-999: 7.96 (6.27, 10.09) ACR ≥1000: 14.61 (11.16, 19.13) **PCR (mg/g)** 50-599: 3.18 (1.40, 7.18) 500-1499: 16.38 (1.34, 30.34) ≥1500: 9.47 (1.81, 49.60) **Dipstick category** +: 2.92 (2.08, 4.10) ++: 7.70 (4.52, 13.10) +++: 15.01 (8.36, 26.95)	**Source of funding:** KDIGO planning committee and National Kidney Foundation staff participated in study design and data collection. **Additional info:** Confounders adjusted for: Age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, & serum total cholesterol concentration. **Interactions:** Interaction of ofeGFR<15 and end stage renal disease was significant in all 12 included studies.
				Mortality HR (95% CI)	**ACR (mg/g)** ACR 30-299: 1.50 (1.28, 1.75)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	(Van Zuilen et al. 2008) Nephro Test (Moranne et al. 2009) RENAAL (Brenner et al. 2001) Steno (Hovind et al. 2004) **Cohorts with PCR:** AASK (Wright et al. 2002) Grampian-PCR (Clark et al. 2007) MDRD (Menon et al. 2008) MMKD (Dieplinger et al. 2009) REIN (Ruggenenti et al. 2001)	analysis.	disease (CVD) was defined as previous myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication. Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Diabetes mellitus defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, or use		ACR 300-999: 1.85 (1.08, 3.16) ACR ≥1000: 2.73 (1.74, 4.26) **PCR (mg/g)** 50-599: 1.08 (0.53, 2.18) 500-1499: 1.81 (1.30, 2.53) ≥1500: 1.72 (0.90, 3.29) **Dipstick category** +: 1.46 (1.24, 1.71) ++: 1.80 (1.38, 2.35) +++: 2.26 (1.68, 3.04)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	REIN 2 (Ruggenenti et al. 2005) **Cohorts with dipstick proteinuria:** Kaiser Permanente Northwest (Johnson et al. 2007)		of glucose lowering drugs or self-reported diabetes. Smoking status was dichotomised as current versus non current smoking. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Cox proportional hazard ratios (HRs) were calculated for each category of eGFR (15-29, 30-44, 45-74, 75-89, 90-104 and ≥105ml/min/1.73m^2) relative to the reference group of 45-74ml/min/1.73m^2, and for each category of ACR/PCR/dipstick proteinuria (using the lowest category for each as the reference). These were adjusted for age, sex,			

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
			race, history of cardiovascular disease, systolic blood pressure, diabetes, concentration of serum total cholesterol and smoking.			

Table 37: FOX2012

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
Caroline S. Fox, Kunihiro Matsushita, Mark Woodward, Henk J. G. Bilo, John Chalmers, Hiddo J. L. Heerspink, Brian J. Lee, Robert M. Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A. Vassalotti, KazumasaYamagishi,	1,024,977 participants: 128,505 (13%) with diabetes 23 general population cohorts, 7 high risk and 15 CKD cohorts were included. **General population cohorts:** Aichi ARIC AusDIab Beaver Dam CKD Beijing CHS COBRA	**Study type:** IPD meta-analysis **Inclusion:** Studies that had at least 1000 participants (not applied to studies that predominantly included patients with CKD), baseline information about eGFR and albuminuria, and at least 50 events for each outcome of interest.	GFR was calculated using the CKD Epidemiology Collaboration equation. Studies were included in which assessed proteinuria with the urine albumin to creatinine ratio (ACR), urine albumin excretion rate, urine protein to creatinine ratio (PCR), or quantitative dipstick protein were measured. Diabetes defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose	**End stage renal disease** Defined as start of renal replacement therapy or death because of kidney disease other than AKI	**With diabetes** **Any eGFR** ACR <30: Reference ACR 30-299: 1.60 [0.85, 2.35] ACR 300-999: 3.55 [2.89, 4.21] ACR ≥1000: 6.79 [4.36, 9.22] **eGFR<15** ACR <10: 1.74 [0.23, 13.16] ACR 10-29: 34.70 [4.21, 286.01] ACR 30-299: 122.00 [4.64, 3207.41] ACR ≥300: 35.70 [21.50, 59.28] **eGFR 15-29** ACR <10: 2.98 [1.68,	**Without diabetes** **Any eGFR** ACR <30: Reference ACR 30-299: 1.86 [1.32, 2.40] ACR 300-999: 2.70 [1.78, 3.62] ACR ≥1000: 5.56 [3.44, 7.68] **eGFR<15** ACR <10: 3.97 [1.58, 9.98] ACR 10-29: 16.00 [11.50, 22.26] ACR 30-299: 22.70 [16.10, 32.01] ACR ≥300: 31.80 [18.90, 53.51] **eGFR 15-29** ACR <10: 6.15 [3.17,	**Source of funding** US National Kidney Foundation **Confounding factors adjusted for:** Age, sex, ethnicity (black vs.non-black), smoking, systolic blood pressure, total cholesterol, body-mass index, history of cardiovascular disease, and albuminuria. **Other information:** Participants with diabetes were generally older

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
Josef Coresh, Paul E. de Jong, Chi Pang Wen, Robert G. Nelson, and Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without	ESTHER Framingham Gubbio HUNT IPHS MESA MRC NHANES III Ohasama PREVEND RanchoBernardo REGARDS Severance Taiwan ULSAM **High risk cohorts:** ADVANCE CARE KEEP KP Hawaii MRFIT	Analysis restricted to participants aged at least 18 years. **Exclusion:** Not stated.	concentration 11.1 mmol/L or more, at least 6.5% use of glucose lowering drugs, or self-reported diabetes. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, coronary revascularisation, heart failure or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication.		5.29] ACR 10-29: 8.25 [5.19, 13.11] ACR 30-299: 23.70 [8.09, 69.43] ACR ≥300: 33.70 [13.80, 82.29] **eGFR 30-44** ACR <10: 2.11 [1.26, 3.53] ACR 10-29: 3.35 [2.07, 5.42] ACR 30-299: 5.71 [3.57, 9.13] ACR ≥300: 8.56 [5.27, 13.90] **eGFR 45-74** ACR <10: Reference ACR 10-29: 1.76 [1.05, 2.95] ACR 30-299: 2.84 [1.11, 7.27] ACR ≥300: 8.01 [3.62,	11.93] ACR 10-29: 7.94 [5.93, 10.63] ACR 30-299: 11.90 [7.17, 19.75] ACR ≥300: 28.90 [10.50, 79.54] **eGFR 30-44** ACR <10: 1.42 [0.85, 2.37] ACR 10-29: 3.01 [2.23, 4.06] ACR 30-299: 4.20 [3.04, 5.80] ACR ≥300: 6.76 [4.90, 9.33] **eGFR 45-74** ACR <10: Reference ACR 10-29: 1.69 [1.23, 2.32] ACR 30-299: 2.85 [1.22, 6.66] ACR ≥300: 3.93 [2.78,	than those without and had a higher prevalence of hypertension, hyperchloesterolaemia and cardiovascular disease. **Interactions:** Interaction of diabetes between those with and those without averaged across full range of eGFR for a 15ml/min / 1.73m^2 reduction was not significant for all-cause or cardiovascular mortality.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
diabetes: a meta-analysis. Lancet 380 (9854):1662-1673, 2012.	Pima ZODIAC **CKD cohorts:** AASK BCCKD Geisinger ACR Geisinger Dip GLOMMS-1 ACR GLOMMS-1 PCR KPNW MASTERPLAN MDRD MMKD NephroTest RENAAL STENO Sunnybrook		Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Smoking status was defined as present, former or never.		17.72] **eGFR ≥75** ACR <10: 1.47 [0.63, 3.43] ACR 10-29: 2.47 [1.29, 4.73] ACR 30-299: 3.43 [1.58, 7.45] ACR ≥300: 4.42 [2.20, 8.88]	5.56] **eGFR ≥75** ACR <10: 0.54 [0.07, 4.17] ACR 10-29: 0.68 [0.38, 1.22] ACR 30-299: 0.74 [0.33, 1.66] ACR ≥300: 1.59 [0.54, 4.68]	
				All-cause mortality	**With diabetes** **Any eGFR** ACR <10: Reference ACR 10-29: 1.35 [1.27, 1.43] ACR 30-299: 1.73 [1.61, 1.85] ACR ≥300: 2.67 [2.31, 3.03] **eGFR<15** ACR <10: 12.00 [3.02, 47.68]	**Without diabetes** **Any eGFR** ACR <30: Reference ACR 10-29: 1.31 [1.23, 1.39] ACR 30-299: 1.67 [1.54, 1.80] ACR ≥300: 2.38 [2.07, 2.69] **eGFR<15** ACR <10: 6.55 [3.53, 12.15]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR 10-29: 5.88 [2.43, 14.23] ACR 30-299: 9.55 [4.53, 20.13] ACR ≥300: 14.50 [8.84, 23.78] **eGFR 15-29** ACR <10: 2.69 [1.78, 4.07] ACR 10-29: 3.30 [2.43, 4.48] ACR 30-299: 4.96 [3.19, 7.71] ACR ≥300: 6.80 [4.76, 9.71] **eGFR 30-44** ACR <10: 1.81 [1.35, 2.43] ACR 10-29: 2.25 [1.87, 2.71] ACR 30-299: 3.13 [2.57, 3.81] ACR ≥300: 4.61 [3.64,	ACR 10-29: 8.56 [5.72, 12.81] ACR 30-299: 6.91 [4.67, 10.22] ACR ≥300: 12.00 [8.84, 16.29] **eGFR 15-29** ACR <10: 3.16 [2.25, 4.44] ACR 10-29: 4.01 [2.86, 5.62] ACR 30-299: 3.90 [2.93, 5.19] ACR ≥300: 6.69 [4.94, 9.06] **eGFR 30-44** ACR <10: 1.71 [1.44, 2.03] ACR 10-29: 2.54 [2.26, 2.85] ACR 30-299: 2.89 [2.31, 3.62] ACR ≥300: 4.00 [2.92,	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					5.84] **eGFR 45-59** ACR <10: 1.15 [1.01, 1.31] ACR 10-29: 1.82 [1.60, 2.07] ACR 30-299: 1.97 [1.65, 2.35] ACR ≥300: 3.23 [2.51, 4.16] **eGFR 60-74** ACR <10: 0.99 [0.92, 1.07] ACR 10-29: 1.32 [1.16, 1.50] ACR 30-299: 1.86 [1.60, 2.16] ACR ≥300: 2.98 [2.36, 3.76] **eGFR 75-89** ACR <10: 0.94 [0.87, 1.02]	5.48] **eGFR 45-59** ACR <10: 1.22 [1.09, 1.37] ACR 10-29: 1.70 [1.49, 1.94] ACR 30-299: 2.10 [1.75, 2.52] ACR ≥300: 3.15 [2.44, 4.07] **eGFR 60-74** ACR <10: 1.01 [0.95, 1.07] ACR 10-29: 1.38 [1.20, 1.59] ACR 30-299: 1.86 [1.64, 2.11] ACR ≥300: 2.41 [1.88, 3.09] **eGFR 75-89** ACR <10: 0.94 [0.89, 0.99]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR 10-29: 1.33 [1.16, 1.52] ACR 30-299: 1.59 [1.35, 1.87] ACR ≥300: 2.42 [1.89, 3.10]	ACR 10-29: 1.30 [1.18, 1.43] ACR 30-299: 1.60 [1.40, 1.83] ACR ≥300: 2.57 [1.98, 3.34]	
					eGFR 90-104 ACR <10: Reference ACR 10-29: 1.41 [1.24, 1.60] ACR 30-299: 1.73 [1.45, 2.06] ACR ≥300: 2.95 [2.22, 3.92]	**eGFR 90-104** ACR <10: Reference ACR 10-29: 1.47 [1.32, 1.64] ACR 30-299: 1.82 [1.64, 2.02] ACR ≥300: 3.23 [2.39, 4.37]	
					eGFR ≥105 ACR <10: 1.27 [1.07, 1.51] ACR 10-29: 1.58 [1.29, 1.94] ACR 30-299: 2.43 [1.90, 3.11] ACR ≥300: 4.38 [2.97, 6.46]	**eGFR ≥105** ACR <10: 1.27 [1.14, 1.41] ACR 10-29: 1.62 [1.35, 1.94] ACR 30-299: 2.39 [2.03, 2.81] ACR ≥300: 5.40 [3.33, 8.76]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
				Cardiovascular mortality Defined as deaths due to myocardial infarction, heart failure, sudden cardiac death, or stroke.	**With diabetes** **Any eGFR** ACR <10: Reference ACR 10-29: 1.43 [1.25, 1.61] ACR 30-299: 1.81 [1.62, 2.00] ACR ≥300: 2.44 [1.99, 2.89] **eGFR<15** ACR <10: 19.90 [1.79, 221.25] ACR 10-29: Not estimable ACR 30-299: Not estimable ACR ≥300: 21.60 [4.65, 100.34] **eGFR 15-29** ACR <10: 4.10 [1.75, 9.61] ACR 10-29: 3.39 [1.56,	**Without diabetes** **Any eGFR** ACR <10: Reference ACR 10-29: 1.38 [1.26, 1.50] ACR 30-299: 1.72 [1.51, 1.93] ACR ≥300: 2.33 [1.92, 2.74] **eGFR<15** ACR <10: 9.63 [2.29, 40.49] ACR 10-29: 15.30 [7.56, 30.97] ACR 30-299: 8.46 [5.04, 14.20] ACR ≥300: 11.90 [7.62, 18.58] **eGFR 15-29** ACR <10: 5.44 [3.11, 9.52] ACR 10-29: 7.12 [3.12,	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					7.37] ACR 30-299: 5.64 [2.64, 12.05] ACR ≥300: 7.96 [4.89, 12.96]	16.25] ACR 30-299: 3.35 [2.34, 4.80] ACR ≥300: 8.91 [4.31, 18.42]	
					eGFR 30-44 ACR <10: 2.12 [1.55, 2.90] ACR 10-29: 2.49 [1.62, 3.83] ACR 30-299: 3.62 [2.50, 5.24] ACR ≥300: 5.57 [4.08, 7.60]	**eGFR 30-44** ACR <10: 2.51 [2.05, 3.07] ACR 10-29: 2.99 [2.07, 4.32] ACR 30-299: 3.52 [2.76, 4.49] ACR ≥300: 5.21 [3.28, 8.28]	
					eGFR 45-59 ACR <10: 1.33 [1.05, 1.68] ACR 10-29: 1.75 [1.31, 2.34] ACR 30-299: 2.27 [1.70, 3.03] ACR ≥300: 3.24 [2.41, 4.36]	**eGFR 45-59** ACR <10: 1.52 [1.30, 1.78] ACR 10-29: 2.19 [1.86, 2.58] ACR 30-299: 2.57 [1.93, 3.42] ACR ≥300: 3.74 [2.73, 5.12]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					eGFR 60-74 ACR <10: 1.25 [1.06, 1.47] ACR 10-29: 1.56 [1.21, 2.01] ACR 30-299: 2.53 [2.00, 3.20] ACR ≥300: 3.21 [2.42, 4.26] **eGFR 75-89** ACR <10: 1.04 [0.88, 1.23] ACR 10-29: 1.70 [1.29, 2.24] ACR 30-299: 1.79 [1.41, 2.27] ACR ≥300: 2.69 [1.91, 3.79] **eGFR 90-104** ACR <10: Reference ACR 10-29: 1.28 [0.95, 1.72]	**eGFR 60-74** ACR <10: 1.14 [1.00, 1.30] ACR 10-29: 1.49 [1.17, 1.90] ACR 30-299: 2.17 [1.88, 2.50] ACR ≥300: 2.38 [1.78, 3.18] **eGFR 75-89** ACR <10: 1.01 [0.91, 1.12] ACR 10-29: 1.46 [1.21, 1.76] ACR 30-299: 1.80 [1.51, 2.15] ACR ≥300: 2.53 [2.03, 3.15] **eGFR 90-104** ACR <10: Reference ACR 10-29: 1.62 [1.31, 2.00]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR 30-299: 1.74 [1.28, 2.37] ACR ≥300: 3.03 [1.90, 4.83] **eGFR ≥105** ACR <10: 1.19 [0.76, 1.86] ACR 10-29: 1.93 [1.12, 3.33] ACR 30-299: 3.00 [1.49, 6.04] ACR ≥300: 5.07 [1.86, 13.82]	ACR 30-299: 1.79 [1.43, 2.24] ACR ≥300: 3.39 [2.12, 5.42] **eGFR ≥105** ACR <10: 1.22 [0.98, 1.52] ACR 10-29: 1.82 [1.14, 2.91] ACR 30-299: 4.00 [2.82, 5.67] ACR ≥300: 7.04 [2.83, 17.51]	

Table 38: GANSEVOORT2011

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
R. T. Gansevoort, K. Matsushita, Der Van,	173,892 from high risk cohorts. (845,125	**Study type:** **Inclusion (for high risk**	In each cohort, subjects were subdivided according to eGFR and albuminuria. GFR was	**Progression of CKD** Defined as annual decline in eGFR during follow-up of at	**eGFR 15-29** ACR under10: 0.50 [0.40, 0.60] ACR 10-29: 3.10 [1.20, 5.00] ACR 30-299: 9.40 [5.30, 13.50]	**Source of funding** **Confounding factors adjusted**

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
V, B. C. Astor, M. Woodward, A. S. Levey, P. E. D. Jong, and J. Coresh. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population	participants from 9 general population cohorts – data not reported in this review). 8 high risk cohorts – (risk of developing CKD) **Cohorts with ACR data:** **Cohorts with dipstick data:**	**cohorts only):** Prospective ccohorts of individuals selected because of high risk of CKD, including patients with cardiovascular disease risk factors (such as hypertension and diabetes) or a history of cardiovascular disease, because screening for CKD is recommended in these groups. Studies had to have information at	estimated using the MDRD equation. Each participating study was asked to standardize their serum creatinine to isotope dilution mass spectrometry-traceable methods, but calibration methods were not uniform. Albuminuria was assessed as the albumin to creatinine ration. If first morning voids were not available, spot urine samples or samples from 24hour urine collections were used. In studies in which no quantitative albuminuria measurements were available, data urine PCR or dipstick testing	least 2.5ml/min/1.73m^2 per year and a last e GFR being less than 45ml/min/1.73m^2, independent of baseline eGFR. Hazard ratio (95% CI)	ACR over300: 38.60 [15.70, 61.50] **eGFR 30-44** ACR <10: 3.30 [2.70, 3.90] ACR 10-29: 3.40 [2.50, 4.30] ACR 30-299: 9.80 [6.30, 13.30] ACR over300: 68.70 [57.60, 79.80] **eGFR 45-59** ACR <10: 3.00 [2.10, 3.90] ACR 10-29: 4.80 [3.70, 5.90] ACR 30-299: 10.10 [4.90, 15.30] ACR over300: 31.40 [16.10, 46.70] **eGFR 60-74** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.80 [1.30, 4.30] ACR over300: 9.30 [6.00, 12.60] **eGFR 75-89** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.00 [0.80, 1.20]	**for:** Age, sex, race and cardiovascular risk factors (including cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure and serum total cholesterol). **Other information:** High risk cohorts had a higher proportion of males and higher prevalence of cardiovascular risk factors than the general population cohorts. High risk cohorts also had lower

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
cohorts. Kidney Int. 80 (1):93-104, 2011.		baseline on eGFR as well as albuminuria levels; at least 1000 subjects included; information on at least one of the three kidney outcome measures and a minimum of 50 events for that outcome measure. **Exclusion:** Not stated.	for proteinuria were collected. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication. Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of		ACR over300: 3.50 [2.50, 4.50] **eGFR 90-104** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 0.90 [0.70, 1.10] ACR over300: 3.50 [0.50, 6.50] **eGFR>105** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 0.60 [0.50, 0.70] **ACR over300: 4.70 [0.30, 9.10]**	eGFR and higher ACR. Incidence of outcomes were 2-6 fold higher in the high risk cohorts than general population cohorts. **Interactions:** Interaction between eGFR and albuminuria was significant for ESRD in only 1 out of 8 cohorts, for AKI in 3 out of 5 cohorts and for progression of CKD in 4 of 11 cohorts. Significant interaction between eGFR and age was found for
				End stage renal disease Defined as start of renal replacement therapy or death coded as because of kidney disease other than AKI	**eGFR 15-29** ACR <10: 32.60 [4.30, 60.90] ACR 10-29: 308.00 [97.00, 519.00] ACR 30-299: 387.00 [86.90, 687.10] ACR over300: 462.70 [31.60, 893.80] **eGFR 30-44** ACR <10: 23.40 [11.00, 35.80] ACR 10-29: 33.40 [12.90, 53.90] ACR30-299: 56.00 [20.00, 92.00] ACR over300: 139.80 [35.60, 244.00]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
			CVD, and ≥6.0mmol/l for a negative history of CVD. Diabetes mellitus defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, or use of glucose lowering drugs or self-reported diabetes. Smoking status was dichotomised as current versus non current smoking.		**eGFR 45-59** ACR <10: 2.70 [1.70, 3.70] ACR 10-29: 3.80 [1.90, 5.70] ACR 30-299: 14.50 [6.30, 22.70] ACR over300: 55.50 [17.90, 93.10] **eGFR 60-74** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 3.10 [1.80, 4.40] ACR over300: 32.20 [11.80, 52.60] **eGFR 75-89** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.70 [0.90, 2.50] ACR over300: 17.30 [4.00, 30.60] **eGFR 90-104** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.30 [1.00, 3.60] ACR over300: 10.00 [2.10, 17.90]	ESRD in only 1 out of 9 cohorts, for AKI in 3 out of 5 cohorts and for progression of CKD in 4 of 11 cohorts. Meta-regression was performed to test association between eGRF and ACR ratio with outcomes differed by the proportion of diabetic participants within each high risk cohort. Proportion of diabetic participants was not significantly associated with the hazard ratio for ESRD associated with eGFR or ACR, or with progression

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					eGFR>105 ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.10 [0.80, 1.40] ACR over300: 2.00 [0.90, 3.10]		of CKD associated with eGFR or ACR. There were too few cohorts with sufficient events to allow meta-regression models for AKI.
				ESRD by Age	**Aged <65 years** **eGFR 15-29** ACR <10: Not estimable ACR 10-29: 656.00 [172.00, 2501.95] ACR 30-299: 792.00 [210.00, 2986.97] ACR over300: 998.00 [105.00, 9485.75] **eGFR 30-44** ACR <10: 15.90 [1.90, 133.06] ACR 10-29: 73.60 [20.50, 264.24] ACR30-299: 90.90 [27.60, 299.38]	**Aged >65 years** **eGFR 15-29** ACR <10: 25.00 [3.20, 195.31] ACR 10-29: 175.00 [42.50, 720.59] ACR 30-299: 125.00 [43.00, 363.37] ACR over300: 506.00 [158.00, 1620.48] **eGFR 30-44** ACR <10: 16.10 [6.70, 38.69] ACR 10-29: 18.10 [7.50, 43.68] ACR30-299: 24.30 [9.30, 63.49]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR over300: 161.00 [26.30, 985.59] **eGFR 45-59** ACR <10: 92.70 [1.40, 6138.06] ACR 10-29: 5.30 [2.30, 12.21] ACR 30-299: 16.90 [4.70, 60.77] ACR over300: 66.90 [20.10, 222.67] **eGFR 60-74** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 4.00 [2.00, 8.00] ACR over300: 39.00 [10.30, 147.67] **eGFR 75-89** ACR <10: Reference ACR 10-29:	ACR over300: 92.70 [46.30, 185.60] **eGFR 45-59** ACR <10: 2.80 [1.10, 7.13] ACR 10-29: 1.80 [0.50, 6.48] ACR 30-299: 10.00 [5.50, 18.18] ACR over300: 31.20 [10.90, 89.31] **eGFR 60-74** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.70 [0.60, 4.82] ACR over300: 20.70 [9.40, 45.58] **eGFR 75-89** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.90	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					Reference ACR 30-299: 1.70 [0.80, 3.61] ACR over300: 16.30 [2.30, 115.52] **eGFR 90-104** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.60 [1.00, 6.76] ACR over300: 10.50 [2.00, 55.12] **eGFR>105** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 1.10 [0.80, 1.51] ACR over300: 1.40 [0.90, 2.18]	[0.60, 6.02] ACR over300: 16.20 [3.10, 84.66] **eGFR 90-104** ACR <10: Reference ACR 10-29: Reference ACR 30-299: Not estimable ACR over300: 15.50 [2.00, 120.12] **eGFR>105** ACR <10: Reference ACR 10-29: Reference ACR 30-299: Not estimable ACR over300: 20.60 [2.40, 176.82]	
				AKI Defined as ICD-9	**eGFR 15-29** ACR <10: 12.30 [5.40, 19.20]		

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
				code 584 as primary or additional discharge code	ACR 10-29: 1.60 [0.00, 3.20] ACR 30-299: 25.30 [13.70, 36.90] ACR over300: 13.70 [0.00, 27.40] **eGFR 30-44** ACR <10: 8.00 [5.40, 10.60] ACR 10-29: 7.50 [5.30, 9.70] ACR 30-299: 14.30 [11.20, 17.40] ACR over300: 26.90 [12.30, 41.50] **eGFR 45-59** ACR <10: 1.70 [1.20, 2.20] ACR 10-29: 3.50 [2.60, 4.40] ACR 30-299: 6.60 [5.20, 8.00] ACR over300: 13.00 [9.70, 16.30] **eGFR 60-74** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.80 [1.40, 4.20] ACR over300: 6.30 [4.30, 8.30] **eGFR 75-89** ACR <10: Reference	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
					ACR 10-29: Reference ACR 30-299: 1.80 [1.30, 2.30] ACR over300: 5.20 [3.20, 7.20] **eGFR 90-104** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.10 [1.30, 2.90] ACR over300: 3.40 [1.40, 5.40] **eGFR>105** ACR <10: Reference ACR 10-29: Reference ACR 30-299: 2.20 [1.20, 3.20] ACR over300: 3.80 [1.20, 6.40]	

Table 39: Hallan et al. 2012 [243]

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
SI Hallan, K Matsushita, Y Sang et al. Age and association of kidney measures with mortality and end-stage renal disease. JAMA 308 (22):2349-2360, 2012.	2,051,244 from general population and high risk cohorts. 38,612 from CKD cohorts. General population and high risk cardiovascular cohorts: Aichi AKDN ARIC AusDIab Beaver Dam CKD Beijing CHS CIRCS COBRA ESTHER Framingham	**Study type:** IPD meta-analysis **Inclusion** Prospective cohorts of people from heheral, high risk (of vascular disease) and CKD populations with baseline information on eGFR and albuminuria, at least 1000 participants (not CKD cohorts) and at least 50 events for any	The CKD-EPI equation with serum creatinine values standardised to isotope dilution mass spectrometry traceable methods was used to estimate GFR. Albuminuria was preferably measured as albumin creatinine ratio (ACR), but studies with urine protein-creatinine ratio (PCR), or dipstick protein were also included. Information on demographic and cardiovascular risk factors was also obtained for all participants. Age was categorised as	**All-cause mortality** **Interaction of eGFR according to 15ml/min/1.73m^2 decline** Hazard ratio (95% CI)	**18-54 years versus 55-64 years:** 1.22 (1.11, 1.35) P<0.001 I^2 = 84.5% **65-74 years versus 55-64 years:** 0.93 (0.89, 0.98) P=0.003 I^2 = 62.6% **≥75 years versus 55-64 years:** 0.89 (0.84, 0.94) P<0.001 I^2 = 51.8%	**Source of funding** **Confounding factors adjusted for:** Sex, race (black versus non-black) history of cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, serum total cholesterol, BMI, albuminuria and the randomised intervention (for clinical trials). **Other information:** Insufficient
				All-cause mortality **Interaction of ACR according to 10 fold increase** **Hazard ratio (95% CI)**	**18-54 years versus 55-64 years:** 1.12 (0.96, 1.29) P=0.139 I^2 = 23.8% **65-74 years versus 55-64 years:** 0.92 (0.85, 0.99) P=0.020 I^2 = 4.5% **≥75 years versus 55-64 years:** 0.81 (0.71, 0.92) P=0.002 I^2 = 41%	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Gubbio HUNT IPHS MESA MRC NHANES III Ohasama Okinawa 83 Okinawa 93 PREVEND Rancho Bernardo	outcome of interest during follow-up. The CDK-EPI **Exclusion criteria: Not stated.**	18-54, 55 to 64, 65 to 74 and 75 or more years. Participants with missing values for either eGFR or albuminuria were excluded. Missing values for other adjustment variables were replaced by the cohort mean.	**End stage renal disease** **Interaction of eGFR according to 15ml/min/1.73m^2 decline** Hazard ratio (95% CI)	**18-54 years versus 55-64 years:** 1.10 (0.87, 1.39) P=0.423 I^2 = 54.1% **65-74 years versus 55-64 years:** 0.84 (0.67, 1.04) P=0.113 I^2 = 36.2% **≥75 years versus 55-64 years:** 0.77 (0.36, 1.65) P<0.505 I^2 = 82.2%	information was presented in the study for hazard ratios at each eGFR and ACR category to add to a forest plot (no confidence intervals presented nor number at risk on Kaplan Meier curves) therefore only interaction at various age ranges can be presented. The Cox proportional hazard ratios (HRs) were calculated with eGFR of 80ml/min/1.73m^2 as the stable reference group or 50ml/min/1.73m^2 for all CKD
	REGARDS Severance Taiwan ULSAM High risk: ADVANCE AKDN (ACR) CARE KEEP KP Hawaii MRFIT Pima			**End stage renal disease** **Interaction of ACR according to 10 fold increase** **Hazard ratio (95% CI)**	**18-54 years versus 55-64 years:** 0.75 (0.42, 1.33) P=0.318 I^2 = 70.3% **65-74 years versus 55-64 years:** 0.89 (0.64, 1.25) P=0.502 I^2 = 36.9% **≥75 years versus 55-64 years:** 0.88 (0.43, 1.80) P=0.73 I^2 = 75.9%	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	ZODIAC 13 CKD cohorts: AASK BC CKD CRIB Geisinger GLOMMS-1 KPNW MASTERPLAN MDRD MMKD NephroTest RENAAL STENO Sunnybrook					cohorts, and ACR <10mg/g or <20mg/g for CKD cohorts. **Interactions:** Evaluated as the ratio of HRs in each age category compared with the age category of 55 to 64 years at each 1 ml/min/1.73m^2 of eGFR from 150 to 120. All-cause mortality: Age interaction was significant for a broad range of eGFRs, and was significant in all categories compared with 55 to 64 years

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
						(P<0.004). Age interaction with ACR less evidence. Overall interaction only reached significance for 65-74years (P=0.02) and 75 years and older (P=0.002). For ESRD overall interactions for eGFR and ACR were not significant in the age categories of 18-54, 65 to 74 and 75 years or older. For CKD cohorts: Mortality did not interact with age, ESRD was borderline

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
						significant (P=0.04 for age 18-54 years, P=0.07 for 65-74 years and P=0.08 for ≥75years versus 55-64 years).

Table 40: MAHMOODI2012

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
B. K. Mahmoodi, K. Matsushita, M. Woodward, P. J. Blankestijn, M. Cirillo, T. Ohkubo, P. Rossing, M. J. Sarnak, B. Stengel, K. Yamagishi, K. Yamashita, L. Zhang, J. Coresh, P. E. de Jong, and B. C. Astor.	742,240 participants without hypertension and 347 256 with hypertension from 25 general population cohorts, 7 high risk cohorts. 21072 participants without hypertension and 17,088 people with hypertension from 13 chronic kidney disease cohorts. **General population**	**Study type:** IPD meta-analysis **Inclusion:** Studies with at least 1000 participants (not applied to studies that predominantly included patients with CKD), baseline information about eGFR and albuminuria, and either mortality or end stage renal disease with a	GFR was estimated using the CKD Epidemiology Collaboration equation, based on age, sex, race and serum creatinine concentration. Studies were included in which assessed proteinuria with the urine albumin to creatinine ratio (ACR), urine albumin excretion rate, urine protein to creatinine ratio (PCR), or quantitative dipstick protein	**End stage renal disease** Defined as start of renal replacement therapy or death because of kidney disease other than AKI.	**Without hypertension** **Any eGFR** ACR <30: Reference ACR 30-299: 2.27 [1.58, 2.96] ACR 300-999: 3.88 [2.17, 5.59] ACR ≥1000: 7.08 [4.02, 10.14] **eGFR<15** ACR <10: Not estimable ACR 10-29: 14.40 [9.24, 22.44] ACR 30-299: 23.90 [15.50, 36.85] ACR ≥300: 34.10 [22.30, 52.14]	**With hypertension** **Any eGFR** ACR <30: Reference ACR 30-299: 1.86 [1.52, 2.20] ACR 300-999: 2.94 [2.35, 3.53] ACR ≥1000: 5.80 [3.86, 7.74] **eGFR<15** ACR <10: 6.26 [2.61, 15.02] ACR 10-29: 17.50 [12.20, 25.10] ACR 30-299: 30.30 [20.60, 44.57] ACR ≥300: 28.70 [17.40, 47.34]	**Source of funding** Data coordinating centre funded by a programme grant from the US National Kidney Foundation (funding sources include Abbott and Amgen). Various sources supported enrolment and data collection **Confounding factors adjusted for:** Age, sex, race (black vs.non-black), history of cardiovascular disease, diabetes, serum total cholesterol, body mass index, smoking and albuminuria.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. Lancet Epub, 2012.	**cohorts:** Aichi ARIC AusDiab Beaver Dam CKD Beijing CHS CIRCS COBRA ESTHER Framingham Gubbio HUNT IPHS MESA MRC NHANES III Ohasama Okinawa 83 Okinawa 93 PREVEND RanchoBernardo REGARDS	minimum of 50 events. Analysis restricted to participants aged at least 18 years. **Exclusion:** Not stated.	were measured. Diabetes defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, at least 6.5% use of glucose lowering drugs, or self-reported diabetes. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, coronary revascularisation, heart failure or stroke. Hypertension		**eGFR 15-29** ACR <10: 5.45 [2.81, 10.57] ACR 10-29: 12.50 [6.41, 24.38] ACR 30-299: 27.00 [8.66, 84.18] ACR ≥300: 50.60 [15.10, 169.58] **eGFR 30-44** ACR <10: 1.88 [0.67, 5.28] ACR 10-29: 5.65 [2.11, 15.13] ACR 30-299: 8.57 [3.24, 22.67] ACR ≥300: 17.10 [6.52, 44.84] **eGFR 45-74** ACR <10: Reference ACR 10-29: 2.61 [1.17, 5.82] ACR 30-299: 4.90	**eGFR 15-29** ACR <10: 5.45 [2.97, 10.00] ACR 10-29: 9.41 [6.33, 13.99] ACR 30-299: 21.40 [10.40, 44.04] ACR ≥300: 44.10 [15.90, 122.32] **eGFR 30-44** ACR <10: 1.96 [1.33, 2.89] ACR 10-29: 3.43 [2.11, 5.58] ACR 30-299: 5.08 [3.62, 7.13] ACR ≥300: 15.60 [6.62, 36.76] **eGFR 45-74** ACR <10: Reference ACR 10-29: 1.81 [1.31, 2.50] ACR 30-299: 1.99	**Other information:** The mean age of participants and the prevalence of traditional cardiovascular risk factors, especially diabetes, was higher in hypertensive individuals than in those without hypertension. **Interactions:** Significant interaction identified at eGFR levels of less than 59ml/min/1.73m^2 for all-cause mortality and less than 73ml/min/1.73m^2 for cardiovascular mortality. The overall interaction of hypertension with

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
	Severance Taiwan ULSAM **High risk cohorts:** ADVANCE CARE KEEP KP Hawaii MRFIT Pima ZODIAC **CKD cohorts:** AASK BC CKD CRIB Geisinger ACR Geisinger dipstick GLOMMS-1 ACR LOMMS-1 PCR KPNW MASTERPLAN MDRD		defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication in primary and high risk population cohorts. In CKD cohorts, hypertension was categorised only by systolic and diastolic blood pressure values because antihypertensive drugs were used in at least 97% of participants in 4 cohorts and information not available in one cohort.		[1.80, 13.34] ACR ≥300: 6.12 [3.35, 11.18] **eGFR ≥75** ACR <10: 0.79 [0.32, 1.95] ACR 10-29: 1.48 [0.81, 2.70] ACR 30-299: 1.43 [0.48, 4.26] ACR ≥300: 3.61 [1.89, 6.90]	[1.19, 3.33] ACR ≥300: 6.01 [3.78, 9.56] **eGFR ≥75** ACR <10: 0.53 [0.03, 9.36] ACR 10-29: 0.91 [0.52, 1.59] ACR 30-299: 1.62 [0.86, 3.05] ACR ≥300: 2.40 [0.36, 16.00]	eGFR was significant for all-cause mortality and cardiovascular mortality. Although there was heterogeneity, most cohorts were in agreement with a weaker association for low eGFR in participants with hypertension compared with those without.
				All-cause mortality	**Without hypertension** **Any eGFR** ACR <10: Reference ACR 10-29: 1.31 [1.25, 1.37] ACR 30-299: 1.65 [1.54, 1.76] ACR ≥300: 2.33 [2.07, 2.59]	**With hypertension** **Any eGFR** ACR <30: Reference ACR 10-29: 1.31 [1.19, 1.43] ACR 30-299: 1.73 [1.54, 1.92] ACR ≥300: 2.80 [2.31, 3.29]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
	MMKD Nephro Test RENAAL STEMO Sunnybrook		Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Smoking status was dichotomised as smokers versus former or never smokers.		**eGFR<15** ACR <10: 8.42 [2.94, 24.11] ACR 10-29: 5.98 [3.64, 9.82] ACR 30-299: 7.89 [5.94, 10.48] ACR ≥300: 9.74 [7.24, 13.10] **eGFR 15-29** ACR <10: 2.18 [1.56, 3.05] ACR 10-29: 3.94 [3.15, 4.93] ACR 30-299: 3.70 [2.46, 5.57] ACR ≥300: 5.26 [4.02, 6.88] **eGFR 30-44** ACR <10: 1.53 [1.32, 1.77] ACR 10-29: 2.34 [2.07, 2.65]	**eGFR<15** ACR <10: 5.14 [1.83, 14.44] ACR 10-29: 12.80 [7.28, 22.50] ACR 30-299: 21.10 [6.12, 72.75] ACR ≥300: 25.70 [9.16, 72.11] **eGFR 15-29** ACR <10: 3.55 [2.16, 5.83] ACR 10-29: 4.86 [2.06, 11.46] ACR 30-299: 6.52 [3.86, 11.01] ACR ≥300: 14.80 [7.07, 30.98] **eGFR 30-44** ACR <10: 2.29 [1.82, 2.88] ACR 10-29: 3.17 [2.62, 3.84]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR 30-299: 2.80 [2.25, 3.48] ACR ≥300: 4.24 [3.17, 5.67] **eGFR 45-59** ACR <10: 1.11 [1.01, 1.22] ACR 10-29: 1.62 [1.44, 1.82] ACR 30-299: 1.90 [1.59, 2.27] ACR ≥300: 2.72 [2.14, 3.46] **eGFR 60-74** ACR <10: 0.99 [0.91, 1.08] ACR 10-29: 1.31 [1.15, 1.49] ACR 30-299: 1.77 [1.57, 2.00] ACR ≥300: 2.32 [1.89, 2.85]	ACR 30-299: 3.89 [2.73, 5.54] ACR ≥300: 5.15 [2.95, 8.99] **eGFR 45-59** ACR <10: 1.35 [1.16, 1.57] ACR 10-29: 1.90 [1.49, 2.42] ACR 30-299: 2.59 [2.02, 3.32] ACR ≥300: 4.12 [2.83, 6.00] **eGFR 60-74** ACR <10: 1.02 [0.94, 1.11] ACR 10-29: 1.30 [1.07, 1.58] ACR 30-299: 1.95 [1.65, 2.30] ACR ≥300: 3.84 [2.37, 6.22]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					eGFR 75-89 ACR <10: 0.94 [0.88, 1.00] ACR 10-29: 1.27 [1.16, 1.39] ACR 30-299: 1.58 [1.40, 1.78] ACR ≥300: 2.18 [1.76, 2.70]	**eGFR 75-89** ACR <10: 0.93 [0.87, 0.99] ACR 10-29: 1.30 [1.11, 1.52] ACR 30-299: 1.72 [1.45, 2.04] ACR ≥300: 2.61 [1.90, 3.59]	
					eGFR 90-104 ACR <10: Reference ACR 10-29: 1.35 [1.23, 1.48] ACR 30-299: 1.73 [1.57, 1.91] ACR ≥300: 2.89 [2.13, 3.92]	**eGFR 90-104** ACR <10: Reference ACR 10-29: 1.52 [1.30, 1.78] ACR 30-299: 1.84 [1.54, 2.20] ACR ≥300: 4.41 [2.97, 6.55]	
					eGFR ≥105 ACR <10: 1.27 [1.15, 1.40] ACR 10-29: 1.45 [1.26, 1.67] ACR 30-299: 2.40	**eGFR ≥105** ACR <10: 1.22 [1.12, 1.33] ACR 10-29: 1.63 [1.40, 1.90] ACR 30-299: 2.94	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					[1.90, 3.03] ACR ≥300: 3.62 [2.42, 5.42]	[1.98, 4.37] ACR ≥300: 8.00 [4.36, 14.68]	
				Cardiovascular mortality Defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death.	**Without hypertension** **Any eGFR** ACR <10: Reference ACR 10-29: 1.38 [1.26, 1.50] ACR 30-299: 1.79 [1.58, 2.00] ACR ≥300: 2.33 [1.99, 2.67] **eGFR<15** ACR <10: Not estimable ACR 10-29: 7.40 [2.74, 19.99] ACR 30-299: 8.57 [4.20, 17.49] ACR ≥300: 7.75 [4.63, 12.97] **eGFR 15-29**	**With hypertension** **Any eGFR** ACR <10: Reference ACR 10-29: 1.50 [1.29, 1.71] ACR 30-299: 2.04 [1.74, 2.34] ACR ≥300: 3.26 [2.32, 4.20] **eGFR<15** ACR <10: 2.60 [0.33, 20.49] ACR 10-29: 33.00 [10.50, 103.72] ACR 30-299: 8.59 [2.57, 28.71] ACR ≥300: 14.10 [5.20, 38.23] **eGFR 15-29**	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR <10: 2.96 [1.52, 5.76] ACR 10-29: 2.35 [1.35, 4.09] ACR 30-299: 6.38 [4.73, 8.61] ACR ≥300: 6.38 [4.73, 8.61] **eGFR 30-44** ACR <10: 1.93 [1.66, 2.24] ACR 10-29: 2.85 [2.10, 3.87] ACR 30-299: 3.70 [2.92, 4.69] ACR ≥300: 5.36 [4.21, 6.82] **eGFR 45-59** ACR <10: 1.35 [1.22, 1.49] ACR 10-29: 1.81 [1.54, 2.13] ACR 30-299: 2.23	ACR <10: 6.94 [4.12, 11.69] ACR 10-29: 11.90 [2.63, 53.84] ACR 30-299: 18.70 [5.33, 65.61] ACR ≥300: 73.60 [15.20, 356.37] **eGFR 30-44** ACR <10: 4.29 [3.39, 5.43] ACR 10-29: 5.31 [3.28, 8.60] ACR 30-299: 5.26 [2.77, 9.99] ACR ≥300: 9.74 [3.74, 25.37] **eGFR 45-59** ACR <10: 1.72 [1.32, 2.24] ACR 10-29: 2.65 [1.75, 4.01] ACR 30-299: 4.57	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					[1.89, 2.63] ACR ≥300: 3.50 [2.42, 5.06] **eGFR 60-74** ACR <10: 1.03 [0.96, 1.11] ACR 10-29: 1.37 [1.20, 1.56] ACR 30-299: 2.10 [1.83, 2.41] ACR ≥300: 2.83 [2.10, 3.81] **eGFR 75-89** ACR <10: 0.98 [0.92, 1.04] ACR 10-29: 1.29 [1.14, 1.46] ACR 30-299: 1.83 [1.50, 2.23] ACR ≥300: 2.54 [1.98, 3.26] **eGFR 90-104**	[3.30, 6.33] ACR ≥300: 8.75 [5.79, 13.22] **eGFR 60-74** ACR <10: 1.23 [1.02, 1.48] ACR 10-29: 1.34 [0.92, 1.95] ACR 30-299: 3.47 [2.67, 4.51] ACR ≥300: 4.47 [2.33, 8.58] **eGFR 75-89** ACR <10: 1.04 [0.92, 1.18] ACR 10-29: 1.64 [1.20, 2.24] ACR 30-299: 2.25 [1.72, 2.94] ACR ≥300: 6.17 [3.68, 10.34] **eGFR 90-104**	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes		Comments
					ACR <10: Reference ACR 10-29: 1.48 [1.17, 1.87] ACR 30-299: 1.67 [1.38, 2.02] ACR ≥300: 2.68 [2.00, 3.59] **eGFR ≥105** ACR <10: 1.32 [1.00, 1.74] ACR 10-29: 1.28 [0.94, 1.74] ACR 30-299: 2.56 [1.82, 3.60] ACR ≥300: 2.34 [1.25, 4.38]	ACR <10: Reference ACR 10-29: 1.54 [1.26, 1.88] ACR 30-299: 1.80 [1.23, 2.63] ACR ≥300: 7.70 [3.17, 18.70] **eGFR ≥105** ACR <10: 1.16 [0.90, 1.50] ACR 10-29: 1.99 [1.28, 3.09] ACR 30-299: 5.47 [3.18, 9.41] ACR ≥300: 13.40 [7.05, 25.47]	

Table 41: VANDERVELDE 2011

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Marije van der Velde, Kunihiro Matsushita, Josef Coresh, Brad C. Astor, Mark Woodward, Andrew Levey, Paul de Jong, Ron T. Gansevoort, Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria	266,975participants 10 high risk cohorts – (risk of developing CKD) Of these, 6 had data on ACR (n=117,500), 4 on dipstick proteinuria (n=149,475) 36.7% with measurement of ACR had CKD according to the definition of eGFR<60ml/min/ 1.73m^2 or ARC ≥30mg/g	**Study type:** IPD meta-analysis Inclusion: Prospective cohort studies; include subjects referred for evaluation of chronic kidney disease risk factors or subjects known to have at least one risk factor defined as a history of cardiovascular disease, diabetes, hypertension, hyperchloesteroemia, or family history of cardiovascular disease; information at baseline on eGFR as well as on albuminuria; at least 1000 subjects included; information on mortality.	In each cohort, subjects were subdivided according to eGFR and albuminuria. GFR was estimated using the MDRD equation. Each participating study was asked to standardize their serum creatinine to isotope dilution mass spectrometry-traceable methods, but calibration methods were not uniform. Albuminuria was assessed as the albumin to creatinine ration. If first morning voids were not available, spot urine samples or samples	**All-cause mortality** Adjusted hazard ratio (95% CI) Compared to ACR 5mg/g	**ACR 10mg/g:** 1.08 (1.01-1.16) **ACR 30mg/g:** 1.38 (1.23-1.56) **ACR 300mg/g:** 2.16 (1.99-2.35)	**Source of funding** KDIGO & US National Kidney Foundation **Confounding factors adjusted for:** Age, sex, race, cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol. For randomised controlled trials, data were also adjusted for treatment arm. **Other information:** The subgroup of people with CKD accounted for 58.6% of all-cause mortality events and
				All-cause mortality Adjusted hazard ratio (95% CI) Stratified by eGFR With ACR data	**ACR 10mg/g** **eGFR>105:** 1.26 (0.97-1.64) **eGFR 90-104: Reference** **eGFR 75-89:** 0.88 (0.70-1.11) **eGFR 60-74:** 0.82 (0.64-1.05) **eGFR 45-59:** 1.16 (0.77-1.73) **eGFR 30-44:** 1.54 (1.11-2.13) **eGFR 15-29:** 2.73 (1.87-3.97) **All:** Reference **ACR 10-29mg/g** **eGFR>105:** 1.31 (1.07-1.60) **eGFR 90-104:** 1.26 (1.05-1.51) **eGFR 75-89:** 1.12 (0.85-1.48) **eGFR 60-74:** 1.18 (0.89-1.56) **eGFR 45-59:** 1.39 (0.97-1.98)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 79 (12):1341-1352, 2011.	**Cohorts with ACR data:** ADVANCE (Patel et al. 2008) AKDN (Hemmelgarn et al. 2010) ONTARGET (Mann et al. 2008) Pima (Pavkov et al. 2008) TRANSCEND (Mann et al. 2009) ZODIAC (Lutgers et al. 2009) **Cohorts with dipstick data:** CARE (Tonelli et al. 2006) KEEP (McCullough et al. 2008)	Exclusion: Not stated	from 24hour urine collections were used. In studies in which no quantitative albuminuria measurements were available, data on dipstick testing for proteinuria were collected. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive		**eGFR 30-44:** 2.06 (1.42-2.97) **eGFR 15-29:**3.52 (2.18-5.69) **All:** 1.28 (1.17-1.39) **ACR 30-299mg/g** **eGFR>105:** 1.51 (1.23-1.84**)** **eGFR 90-104:** 1.63 (1.37-1.95) **eGFR 75-89:** 1.58 (1.36-1.84) **eGFR 60-74:** 1.63 (1.28-2.07) **eGFR 45-59:** 1.96 (1.57-2.43) **eGFR 30-44:** 2.84 (1.98-4.06) **eGFR 15-29:** 3.73 (2.90-4.80) **All:** 1.79 (1.60-2.00) **ACR ≥300** **eGFR >105:** 2.97 (2.19-4.04) **eGFR 90-104:** 2.72 (2.08-3.56) **eGFR 75-89:** 2.91 (2.28-3.73) **eGFR 60-74:** 2.67 (1.76-4.04) **eGFR 45-59:** 3.58 (2.54-5.05) **eGFR 30-44:** 3.99 (2.73-5.83) **eGFR 15-29:** 5.43 (3.94-7.49) **All:** 3.29 (3.04-3.56)	59.4% of cardiovascular mortality events. Baseline characteristics of the dipstick cohorts are generally comparable to the ACR cohorts, although ACR cohorts had a higher percentage of males and people with diabetes or history of cardiovascular disease, and a lower percentage of Blacks. **Interactions:** Interactions (assessed by likelihood-ratios) between eGFR and albuminuria was significant for all-cause mortality in only 4 of 10 cohorts, and for cardiovascular mortality in only 1 of 7 cohorts. Significant interaction
				All-cause	**Dipstick negative**	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	KP Hawaii (Lee & Forbes 2009) MRFIT (Ishani et al. 2006)		medication. Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Diabetes mellitus defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, or use of glucose lowering drugs or self-reported diabetes. Smoking status was dichotomised as current versus non current smoking.	**mortality** Adjusted hazard ratio (95% CI) Stratified by eGFR With dipstick data	**eGFR>105:** 1.08 (0.91-1.27) **eGFR 90-104: Reference** **eGFR 75-89:** 0.82 (0.75-0.90) **eGFR 60-74:** 0.81 (0.73-0.89) **eGFR 45-59:** 0.88 (0.75-1.03) **eGFR 30-44:** 1.18 (0.68-2.06) **eGFR 15-29:** 3.12 (1.53-6.37) **All:** Reference **Dipstick Trace** **eGFR>105:** 1.16 (0.69-1.97) **eGFR 90-104:** 1.09 (0.90-1.32) **eGFR 75-89:** 1.02 (0.86-1.20) **eGFR 60-74:** 0.93 (0.79-1.11) **eGFR 45-59:** 1.05 (0.82-1.36) **eGFR 30-44:** 1.87 (1.30-2.68) **eGFR 15-29:** 4.25 (2.11-8.58) **All:** 1.24 (1.09-1.41) **Dipstick 1+** **eGFR>105:** 2.10 (1.33-3.32) **eGFR 90-104:** 1.63 (1.20-2.21) **eGFR 75-89:** 1.35 (0.88-2.05) **eGFR 60-74:** 1.41 (0.85-2.35)	between eGFR and Age was found in 3 or 10 cohorts for all-cause mortality and in 2 out of 7 cohorts for cardiovascular mortality.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
					eGFR 45-59: 2.25 (1.55-3.25) **eGFR 30-44:** 2.51 (1.78-3.54) **eGFR 15-29:** 3.49 (2.26-5.41) **All:** 1.93 (1.38-2.70) **Dipstick ≥2+** **eGFR >105:** 1.86 (0.63-5.46) **eGFR 90-104:** 3.86 (1.44-10.36) **eGFR 75-89:** 3.22 (1.59-6.52) **eGFR 60-74:** 2.29 (1.32-3.98) **eGFR 45-59:** 2.40 (1.13-5.12) **eGFR 30-44:** 5.50 (3.56-8.50) **eGFR 15-29:** 7.14 (4.64-10.99) **All:** 3.48 (1.75-6.92)	
				Cardiovascular mortality Defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. Adjusted hazard ratio (95% CI)	**ACR 10mg/g:** 1.13 (1.07-1.2) **ACR 30mg/g:** 1.55 (1.30-1.86) **ACR 300mg/g:** 2.59 (1.95-3.44)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
				Compared to ACR 5mg/g		
				Cardiovascular mortality Adjusted hazard ratio (95% CI) Stratified by eGFR With ACR data	**ACR <10mg/g** **eGFR>105:** 1.20 (0.89-1.62) **eGFR 90-104:** Reference **eGFR 75-89:** 1.02 (0.82-1.26) **eGFR 60-74:** 0.86 (0.75-1.00)1.00 (0.81-1.23) **eGFR 45-59:** 1.42 (1.14-1.77) **eGFR 30-44:** 2.27 (1.72-3.01) **eGFR 15-29:** 3.93 (2.10-7.35) **All:** Reference **ACR 10-29mg/g** **eGFR>105:** 1.62 (1.10-2.39) **eGFR 90-104:** 1.56 (1.12-2.17) **eGFR 75-89:** 1.34 (1.03-1.76) **eGFR 60-74:** 1.54 (1.16-2.04) **eGFR 45-59:** 2.06 (1.60-2.66) **eGFR 30-44:** 3.74 (2.06-6.78) **eGFR 15-29:** 5.60 (2.34-13.43) **All:** 1.46 (1.32-1.62)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
					ACR 30-299mg/g **eGFR>105:** 2.04 (1.40-2.95) **eGFR 90-104:** 1.95 (1.44-2.65) **eGFR 75-89:** 1.82 (1.42-2.34) **eGFR 60-74:** 2.01 (1.55-2.59) **eGFR 45-59:** 2.56 (2.03-3.22) **eGFR 30-44:** 3.95 (3.02-5.18) **eGFR 15-29:** 6.06 (3.89-9.45_ **All:** 2.09 (1.73-2.53) **ACR ≥300** **eGFR >105:** 3.55 (1.80-7.01) **eGFR 90-104:** 4.12 (2.50-6.77) **eGFR 75-89:** 4.76 (3.32-6.81) **eGFR 60-74:** 4.00 (2.83-5.66) **eGFR 45-59:** 5.58 (3.19-9.79) **eGFR 30-44:** 6.00 (4.40-8.18) **eGFR 15-29:** 7.21 (4.33-11.99) **All:** 4.02 (3.50-4.62)	
				Cardiovascular mortality Adjusted hazard ratio (95% CI) Stratified by eGFR	**Dipstick Negative** **eGFR>105:** 0.96 (0.73-1.26) **eGFR 90-104:** Reference **eGFR 75-89:** 0.87 (0.75-1.00) **eGFR 60-74:** 0.86 (0.75-1.00)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
				With dipstick data	**eGFR 45-59:** 0.89 (0.79-1.15) **eGFR 30-44:** 0.55 (0.13-2.31) **eGFR 15-29:** Insufficient events for reliable estimate **All:** Reference **Dipstick Trace** **eGFR>105:** 1.07 (0.62-1.83) **eGFR 90-104:** 1.10 (0.81-1.50) **eGFR 75-89:** 1.03 (0.85-1.26) **eGFR 60-74:** 1.05 (0.72-1.54) **eGFR 45-59:** 1.04 (0.65-1.66) **eGFR 30-44:** 1.07 (0.23-5.05) **eGFR 15-29:** Insufficient events for reliable estimate **All:** 1.15 (1.03-1.29) **Dipstick 1+** **eGFR>105:** 3.05 (0.60-15.40) **eGFR 90-104:** 2.07 (1.24-3.46) **eGFR 75-89:** 1.03 (0.72-1.48) **eGFR 60-74:** 1.29 (0.91-1.82) **eGFR 45-59:** 2.70 (1.29-5.68) **eGFR 30-44:** 3.06 (0.81-11.56)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
					eGFR 15-29: Insufficient events for reliable estimate **All:** 1.57 (1.27-1.93) **Dipstick ≥2+** **eGFR>105:** 1.18 (0.29-4.75) **eGFR 90-104:** 2.28 (1.07-4.86) **eGFR 75-89:** 2.82 (1.03-7.70) **eGFR 60-74:** 1.91 (0.96-3.79) **eGFR 45-59:** 1.62 (0.80-3.31) **eGFR 30-44:** 3.45 (1.01-11.76) **eGFR 15-29:** Insufficient events for reliable estimate **All:** 2.30 (1.52-3.50)	

G.4 Cause of CKD – risk factors for adverse outcomes

G.4.1 Diabetes

Table 42: Fox et al. 2012

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect size	Comments
Caroline S. Fox, Kunihiro Matsushita, Mark Woodward, Henk J. G. Bilo, John Chalmers, Hiddo J. L. Heerspink, Brian J. Lee, Robert M. Perkins, Peter Rossing, Toshimi Sairenchi, Marcello	1,024,977 participants: 128,505 (13%) with diabetes 23 general population cohorts, 7 high risk and 15 CKD cohorts were included. **General population cohorts:** Aichi ARIC AusDIab Beaver Dam CKD Beijing CHS	**Study type:** IPD meta-analysis **Inclusion:** Studies that had at least 1000 participants (not applied to studies that predominantly included patients with CKD), baseline information about eGFR and albuminuria, and at least 50 events for each outcome of interest.	GFR was calculated using the CKD Epidemiology Collaboration equation. Studies were included in which assessed proteinuria with the urine albumin to creatinine ratio (ACR), urine albumin excretion rate, urine protein to creatinine ratio (PCR), or quantitative dipstick protein were measured. Diabetes defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, at least 6.5% use of glucose lowering drugs, or self-reported	**End stage renal disease** Defined as start of renal replacement therapy or death because of kidney disease other than AKI Adjusted HR (95% CI), diabetes vs.no diabetes.*	eGFR <30: 1.40 (1.14, 1.73) eGFR 30-44: 1.41 (1.28, 1.55) eGFR 45-60: 1.44 (1.32, 1.58)	**Source of funding** US National Kidney Foundation **Confounding factors adjusted for:** Age, sex, ethnicity (black vs.non-black), smoking, systolic blood pressure, total cholesterol, body-mass index, history of cardiovascular disease, and albuminuria.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect size	Comments
Tonelli, Joseph A. Vassalotti, KazumasaYamagishi, Josef Coresh, Paul E. de Jong, Chi Pang Wen, Robert G. Nelson, and Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-	COBRA ESTHER Framingham Gubbio HUNT IPHS MESA MRC NHANES III Ohasama PREVEND RanchoBernardo REGARDS Severance Taiwan ULSAM **High risk cohorts:** ADVANCE CARE KEEP KP Hawaii MRFIT Pima	Analysis restricted to participants aged at least 18 years. **Exclusion:** Not stated.	diabetes. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, coronary revascularisation, heart failure or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication. Hyperchloesterolemia was defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Smoking status was defined as present, former or never.			**Other information:** * Data provided by CKD prognosis consortium. Participants with diabetes were generally older than those without and had a higher prevalence of hypertension, hyperchloesterolaemia and cardiovascular disease. **Interactions:** Interaction of diabetes between those with and those without averaged across full range of eGFR for a

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect size	Comments
stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 380 (9854):1662-1673, 2012.	ZODIAC **CKD cohorts:** AASK BCCKD Geisinger ACR Geisinger Dip GLOMMS-1 ACR GLOMMS-1 PCR KPNW MASTERPLAN MDRD MMKD NephroTest RENAAL STENO Sunnybrook.					15ml/min/1.73m^2 reduction was not significant for all-cause or cardiovascular mortality.

G.4.2 Hypertension

Table 43: Mahmoodi et al. 2012

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
B. K. Mahmoodi, K. Matsushita, M. Woodward, P. J. Blankestijn, M. Cirillo, T. Ohkubo, P. Rossing, M. J. Sarnak, B. Stengel, K. Yamagishi, K. Yamashita, L. Zhang, J. Coresh, P. E. de Jong, and B. C. Astor. Association	742,240 participants without hypertension and 347 256 with hypertension from 25 general population cohorts, 7 high risk cohorts. 21072 participants without hypertension and 17,088 people with hypertension from 13 chronic kidney disease cohorts. **General population cohorts:** Aichi ARIC AusDiab Beaver Dam CKD Beijing	**Study type:** IPD meta-analysis **Inclusion:** Studies with at least 1000 participants (not applied to studies that predominantly included patients with CKD), baseline information about eGFR and albuminuria, and either mortality or end stage renal disease with a	GFR was estimated using the CKD Epidemiology Collaboration equation, based on age, sex, race and serum creatinine concentration. Studies were included in which assessed proteinuria with the urine albumin to creatinine ratio (ACR), urine albumin excretion rate, urine protein to creatinine ratio (PCR), or quantitative dipstick protein were measured. Diabetes defined as fasting glucose concentration 7.0mmol/L or more, non-fasting glucose concentration 11.1 mmol/L or more, at least 6.5% use of glucose lowering drugs, or self-reported	**End stage renal disease** Defined as start of renal replacement therapy or death because of kidney disease other than AKI. Adjusted HR (95% CI), diabetes vs.no diabetes.*	eGFR <30: 0.72 (0.53, 0.98) eGFR 30-44: 0.94 (0.84, 1.05) eGFR 45-60: 1.08 (0.99, 1.18)	**Source of funding** Data coordinating centre funded by a programme grant from the US National Kidney Foundation (funding sources include Abbott and Amgen). Various sources supported enrolment and data collection **Confounding factors adjusted for:** Age, sex, race (black vs.non-black), history of cardiovascular disease, diabetes, serum total cholesterol, body mass index, smoking and albuminuria.
				All-cause mortality Adjusted HR (95% CI), diabetes vs.no diabetes.*	eGFR <30: 0.78 (0.51, 1.20) eGFR 30-44: 1.10 (0.94, 1.30) eGFR 45-60: 1.22 (1.02, 1.46)	
				Cardiovascular mortality Defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death. Adjusted HR (95% CI),	eGFR <30: 1.39 (0.78, 4.05) eGFR 30-44: 1.06 (0.51, 2.22) eGFR 45-60: -	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
s of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertensi on: a meta-analysis. Lancet Epub, 2012.	CHS CIRCS COBRA ESTHER Framingham Gubbio HUNT IPHS MESA MRC NHANES III Ohasama Okinawa 83 Okinawa 93 PREVEND RanchoBernardo REGARDS Severance Taiwan ULSAM **High risk cohorts:** ADVANCE CARE	minimum of 50 events. Analysis restricted to participants aged at least 18 years. **Exclusion:** Not stated.	diabetes. History of cardiovascular disease (CVD) was defined as previous myocardial infarction, coronary revascularisation, heart failure or stroke. Hypertension defined as systolic blood pressure 140mmHg or more, diastolic blood pressure 90mmHg or more, or use of antihypertensive medication in primary and high risk population cohorts. In CKD cohorts, hypertension was categorised only by systolic and diastolic blood pressure values because antihypertensive drugs were used in at least 97% of participants in 4 cohorts and information not available in one cohort. Hyperchloesterolemia was	diabetes vs.no diabetes.*		**Other information:** ***** Data provided by CKD prognosis consortium. The mean age of participants and the prevalence of traditional cardiovascular risk factors, especially diabetes, was higher in hypertensive individuals than in those without hypertension. **Interactions:** Significant interaction identified at eGFR levels of less than 59ml/min/1.73m^2 for all-cause mortality and less than 73ml/min/1.73m^2 for

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	KEEP KP Hawaii MRFIT Pima ZODIAC **CKD cohorts:** AASK BC CKD CRIB Geisinger ACR Geisinger dipstick GLOMMS-1 ACR LOMMS-1 PCR KPNW MASTERPLAN MDRD MMKD Nephro Test RENAAL STEMO Sunnybrook		defined as total cholesterol ≥5.0 mmol/l in the case of a positive history of CVD, and ≥6.0mmol/l for a negative history of CVD. Smoking status was dichotomised as smokers versus former or never smokers.			cardiovascular mortality. The overall interaction of hypertension with eGFR was significant for all-cause mortality and cardiovascular mortality. Although there was heterogeneity, most cohorts were in agreement with a weaker association for low eGFR in participants with hypertension compared with those without.

G.4.3 Glomerular disease

Table 44: Chou et al. 2012

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Y.-H. Chou, Y.-C. Lien, F.-C. Hu, W.-C. Lin, C.-C. Kao, C.-F. Lai, W.-C. Chiang, S.-L. Lin, T.-J. Tsai, K.-D. Wu, and Y.-M. Chen. Clinical outcomes and predictors for ESRD and mortality in primary GN. Clin.J.Am.Soc. Nephrol. 7 (9):1401-1408, 2012. **Time:** 1993-2006, all patients followed up	**n:** 580 participants **Baseline characteristics** N: 987 Excluded:407 **Total: n=580** Age: 44.4 (16.8) Diabetes, %: 7.9 Hypertension, %:32.5 eGFR (ml/min/1.73m^2),%: ≥90: 27.6 60-89: 34.1 30-59: 25.5 15-29: 8.8 <15: 4.0 Proteinurea, %: -mild (1+ or2+): 28.7 -severe (>3.5g/d or ≥3+): 71.3 Steroid treatment alone, %: 42.0 Cytotoxic treatment alone, %: 1	**Study type:** Retrospective observational **Inclusion:** People aged over 18 years referred to the Taiwan University Hospital between 1993 – 2006 for native kidney biopsy; reason for biopsy included nephrotic syndrome, unexplained renal failure, persistent urinary abnormalities or haematuria. **Exclusion:** people with membrano-proliferative glomerylonephritis, mesiango-proliferative glomerulonephritis, secondary GN or other renal pathologies such as	Data was obtained from databank of National Health Insurance Research Database. Study population cross linked with Taiwan Society of Nephrology registry of 2008. All subjects followed until 2008 for occurrence of primary endpoints such as death from any cause of=r ESRD requiring renal transplantation or long term dialysis. MDRD equation	Time from biopsy to dialysis in years (Kaplan Meier) HR (95% CI) calculated by NCGC from Kaplan Meier curve and number at risk. **Time from biopsy to death**	Events in next period/subjects at risk **MCD - reference** 0: 1/109 3: 0/93 6: 0/61 9: 0/31 12: 0/7 15: 0/1 **MN:** 2.2 (0.64-7.56) **IgAN:** 5.1 (2.4-10.83) **FSGS:** 5.86 (3.07-11.19) **MCD:**	**Source of funding:** Grants from National Taiwan University hospital, Bureau of health promotion, Ta-Tung Kidney Foundation, Mrs Hsiu-Chin Lee Kidney Research Fund, Taipei, Taiwan. **Additional info:** Predictors for ESRD were (all values HR (95%CI): FSGS 34.64 (2.68-447.38), IgAn patients with hypertension (6.92, 1.83-26.22), IgAN patients with higher proteinuria (3.05, 1.68-5.54), MN patients with higher proteinuria (2.98, 1.62-5.47), FSGS patients with higher proteinuria (1.80,

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
until 2008 for primary end points of death or ESRD requiring renal transplantation or long term dialysis	**FSGS: n=132** Age: 44.3 (15.1) Diabetes, %: 8.3 Hypertension, %: 48.5 eGFR (ml/min/1.73m^2)%: ≥90: 13.5 60-89: 25.6 30-59: 39.9 15-29: 16.5 <15: 4.5 Proteinurea, %: -mild (1+ or2+): 31.1 -severe (>3.5g/d or ≥3+): 68.9 Steroid treatment alone, %: 19.7 Cytotoxic treatment alone, %: 1 **IgAN: n=130** Age: 34.5 (12.1) Diabetes, %: 2.3 Hypertension, %: 25.4 eGFR (ml/min/1.73m^2) %: ≥90: 17.7 60-89: 35.4	diabetic nephropathy, lupus nephritis and incomplete laboratory data.	was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. Decline of eGFR calculated by calculating the differences of eGFR normalised by intervals between the time at biopsy and the time at the last clinic visit before occurrence of primary endpoints or end of 2008 **Statistical analysis:** Cox proportional hazard models were constructed using multivariate analysis.	**survival curve (years)** (Kaplan Meier) HR (95% CI) calculated by NCGC from Kaplan Meier curve and number at risk.	Reference **MN:**3.48 (1.75-6.92) **IgAN:**1.95 (0.49-7.76) **FSGS:** 4.04 (1.68-9.72)	1.18-2.73), patients with higher serum albumin (1.74, 1.17-2.60), patients with higher serum creatinine (1.49, 1.25-1.78) and patients with higher serum tryiglycerides (1.003, 1.001-1.004) Predictors for mortality were (all values HR (95%CI): MN with higher proteinuria (1.69, 1.24-2.32), FSGS with higher serum creatinine (1.46, 1.19-1.80), and older age (1.08, 1.06-1.10), MN with higher serum albumin (0.54, 0.33-0.08) Follow-up: 15 years

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	30-59: 29.2 15-29: 8.5 <15: 9.2 Proteinurea, %: -mild (1+ or2+): 56.3 -severe(>3.5g/d or ≥3+):43.7 Steroid treatment alone, %: 30.0 Cytotoxic treatment alone, %:0 **MCD: n=109** Age: 35.7 (15.9) Diabetes, %: 4.6 Hypertension, %: 21.1 eGFR (ml/min/1.73m^2)%: ≥90: 48.6 60-89: 33.1 30-59: 11.9 15-29: 4.6 <15: 1.8 Proteinurea, %: -mild (1+ or2+): 25.9 -severe (>3.5g/d or ≥3+): 74.1 Steroid treatment alone, %: 64.2					

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Cytotoxic treatment alone, %: 0 **MN: n=209** Age: 55.2 (14.3) Diabetes, %: 13.9 Hypertension, %: 33.0 eGFR (ml/min/1.73m^2)%: ≥90: 31.6 60-89: 39.7 30-59: 21.1 15-29: 6.2 <15: 1.4 Proteinurea, %: -mild (1+ or2+): 11.6 -severe (>3.5g/d or ≥3+): 88.4 Steroid treatment alone, %: 52.2 Cytotoxic treatment alone, %: 1					

MCD = minimal change disease, MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis

Table 45: Lee et al. 2013

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Hajeong Lee, Dong Ki Kim, Kook Hwan Oh, Kwon Wook Joo, Yon Su Kim, Dong Wan Chae, Suhnggwon Kim, and Ho Jun Chin. Mortality and renal outcome of primary glomerulonephritis in Korea: observation in 1,943 biopsied cases. Am.J.Nephrol. 37 (1):74-83, 2013. **Setting**: Seoul National University Hospital	**n:** 1,943 participants **Baseline characteristics:** **MCD:** *At biopsy:* N: 187 Age 37 (23-52) (years)median (IQR): Gross haematuria, n(%): 21 m (11.3) Nephrotic syndrome n(%): 120 (67.4) Diabetes n(%): 8 (4.3) Hypertension n(%): 24 (13) eGFR ml/min/1.73m^2(median, IQR): 80.2 (51.2-100.5) Proteinuria, g/day: 7.86 (4.08-12.08) *Follow up:* Diabetes n,%: 14 (7.6) Malignancy, n, %: 20 (10.9) CVD, n,%: 3 (5.9) **FSGS** *At biopsy:* N:251 Age (years)median (IQR): 40 (26-55) Gross haematuria, n(%): 18 (7.2) Nephrotic syndrome n(%): 63 (25.4)	**Study type:** Retrospective cohort **Inclusion:** 4,998 patients older than 15 years underwent percutaneous native kidney biopsy at Seoul National Hospital **Exclusion:** people diagnosed with secondary GN, tuberlointerstitial disease, renal vascular disease, solid organ malignancy, immunoglobulin deposition disease or ESRD. Inadequate specimens and biopsies taken	Baseline data obtained from review of medical records at time of biopsy. MDRD equation was used to estimate GFR after measuring serum creatinine concentration. Data on mortality and cause of death obtained from Korean National Statistical Office. ESRD data collected from Korean ESRD registry. Medical records reviewed retrospectively to obtain additional information related to primary outcome.	**ESRD** progression defined as permanent haemodialysis, peritoneal dialysis or renal transplantation after renal biopsy. Kaplan-meier Cumulative patient survival after ESRD progression HR (95% CI) calculated by NCGC from Kaplan Meier curve and number at risk.	**MCD:** Reference **MN:** 4.3 (1.72-10.75) **IgAN:** 3.05 (1.96-4.75) **FSGS:** 4.42 (2.51-7.78) **MPGN:** 34.65 (9.54-125.85)	**Source of funding:** None **Additional info:** Follow-up: 240 months Unadjusted hazard ratios
				Mortality HR (95% CI) **HR (95% CI) calculated by NCGC from Kaplan Meier curve and number at risk.**	**MCD:** Reference **MN:** 1.41 (0.97-2.05) **IgAN:** 1.08 (0.97-1.20) **FSGS:** 1.41 (0.98-2.03) **MPGN:** 1.80 (0.97-	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Duration: January 1979-December 2008. Median follow up of 90 months (IQR 56-142 months)	Diabetes n(%): 14 (5.6) Hypertension n(%): 89 (35.9) eGFR ml/min/1.73m^2(median, IQR): 42 (40.1-84.5) Proteinuria, g/day: 3.23 (1.70-7.33) *Follow up:* Diabetes n,%: 37 (14.9) Malignancy, n, %: 21 (8.5) CVD, n,%: 4 (11.3) **MN** *At biopsy:* N:232 Age (years)median (IQR): 54 (44-63) Gross haematuria, n(%): 14 (6) Nephrotic syndrome n(%): 102 (44.3) Diabetes n(%): 20 (8.7) Hypertension n(%): 61 (26.6) eGFR ml/min/1.73m^2(median, IQR): 79.3 (60.4-95.5) Proteinuria, g/day: 5.20 (3.13-8.80) *Follow up:* Diabetes n,%:30 (13) Malignancy, n, %: 23 (10) CVD, n,%: 8 (10)	before 1992 also excluded (to maximise completeness of data)	Assumed that patients with no follow up creatinine values who did not undergo renal replacement therapy or a reported death did not meet the primary endpoint. Participants divided into one of 5 major type of GN: MCD (n=187), FSGS (n=251), MN (n=232), IgAN (n=1009), MPGN (n=47) **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Kaplan Meier curves used to estimate survival rates using	Kaplan-meier Cumulative patient or renal survival after renal biopsy	3.34)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	IgAN *At biopsy:* N:1009 Age (years)median (IQR): 35 (26-46) Gross haematuria, n(%): 240 (23.9) Nephrotic syndrome n(%): 16 (4.2) Diabetes n(%): 25 (2.5) Hypertension n(%): 247 (24.6) eGFR ml/min/1.73m^2(median, IQR): 68.9 (49.6-85.5) Proteinuria, g/day: 1.30 (0.60-2.40) *Follow up:* Diabetes n,%: 61 (6.1) Malignancy, n, %: 55 (5.5) CVD, n,%: 9 (4.9) **MPGN** *At biopsy:* N:47 Age (years)median (IQR): 46 (29-60) Gross haematuria, n(%): 6 (12.8) Nephrotic syndrome n(%): 16 (34.8) Diabetes n(%): 3 (6.4) Hypertension n(%): 16 (34)		log-rank test to analyse ESRD progression and patient death. Mortality in GN patients compared to age/sex matched general population-SMR calculated (not reported here)			

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	eGFR ml/min/1.73m^2(median, IQR): 66 (35.5-88.2) Proteinuria, g/day:4.80 (2.14-8.01) *Follow up:* Diabetes n,%: 4 (8.5) Malignancy, n, %: 4 (8.5) CVD, n,%: 1 (12.8)					

MCD = minimal change disease, MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis. MPGN = membranoproliferative glomerulonephritis

Table 46: Moranne et al. 2008

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
O. Moranne, L. Watier, J. Rossert, and B. Stengel. Primary glomerulonephritis: An update on renal survival and determinants of progression. QJM 101 (3):215-224, 2008. **Location:** University Paris Sud, School of medicine. **Duration:** 1994-2001	**n:** 536 participants **Baseline characteristics:** Cases included: 536 Number interviewed:339 Could not attend:88 Died before 2002:18 Lost to follow up:91 **Overall cohort:** N:536 Age (years, mean, SD): 43 (17) Diabetes, %:5 Hypertension (>140-90 or treated):60 eGFR (ml/min/1.73m$^{2)}$ median, IQR):70 (43-91) ≥60:61 30-60:24 15-30:15 Proteinuria (g/L), median, IQR:2.5 (0.9-5.0)	**Study type:** Retrospective cohort **Inclusion:** All white adult patients (>18 years) from 11 Paris area nephrology departments who were first diagnosed with primary IgAN, MN or FSGS between January 1994 ND June 2001. **Exclusion:** HIV, heroin abuse and severe reduction in kidney mass for FSGS; Henoch-Schonen purpura, cirrhosis, GI inflammatory diseases for IgAN and SLE, malignancy, viral hepatitis B and drug toxicity for MN. 26 patients were excluded with an eGFR	Patients were identified from renal biopsy files and affiliated pathology departments; all GNs were histologically proven. Of the 536 cases included, these were invited for interview and blood test between 2002-2004. Nine experts reviewed medical records of 853 patients meeting these criteria and confirmed diagnosis and primary nature of GN for 562. Patients invited for interview and blood test between 2002-2004 MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum	**ESRD** time to first treatment of ESRD, including dialysis or pre-emptive transplantation. End point for sub-cohort was composite of time to either ESRD treatment of halving of eGFR (n=339) HR (95% CI)	**Overall cohort:** **GN type:** IgAN: referent (n=283) MN: 2.6 (0.3-13.0) (n=129) FSGS: 7.0 (2.0-24.0) (n=124) **Sub-cohort (n=339)** **GN type:** IgAN: referent (n=193) MN: 1.9 (0.2-22) (n=76) FSGS:17.0 (4.0-72.0) (n=70)	**Source of funding:** Study supported by grants from ministry of Health, Ministry of environment, ministry of research and biomedicine agency. **Additional info:** Confounders adjusted for: Age, gender, histological type and all baseline covariates except eGFR. **Follow-up:** 7 years

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	%>3: 43 **FSGS:** N: 124 Age (years, mean, SD): 46 (16) Diabetes, %: 10 Hypertension (>140-90 or treated):74 eGFR (ml/min/1.73m$^{2)}$ median, IQR): 56 (36-83) ≥60: 45 30-60: 36 15-30: 19 Proteinuria (g/L), median, IQR: 3.7 (2-6.6) %>3: 61 **MN:** N:129 Age (years, mean, SD): 54 (18) Diabetes, %: 7 Hypertension (>140-90 or treated): 60	<15ml/min/1.73m^2	creatinine concentration. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Cox proportional hazard ratios (HRs) were calculated for ESRD for all GN patients and subgroup of 339 patients who were interviewed. All models adjusted or interaction of age and histological type. Kaplan-Meier used to estimate renal survival probabilities. Patients who died before ESRD were censored			

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	eGFR (ml/min/1.73m$^{2)}$ median, IQR): 79 (61-95) ≥60: 75 30-60: 18 15-30: 7 Proteinuria (g/L), median, IQR: 6.0 (2.3-9) %>3: 84 **IgAN:** N: 283 Age (years, mean, SD): 37 (14) Diabetes, %: 3 Hypertension (>140-90 or treated): 53 eGFR (ml/min/1.73m$^{2)}$ median, IQR): 70 (61-95) ≥60: 62 30-60: 21 15-30: 17 Proteinuria (g/L), median, IQR: 1.2 (0.5-2.5) %>3: 17					

MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis

G.4.4 Acute kidney injury

Table 47: Amdur et al. 2009

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Richard L. Amdur, Lakhmir S. Chawla, Susan Amodeo, Paul L. Kimmel, and Carlos E. Palant. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 76 (10):1089-1097, 2009. **Setting:** United States Department of Veterans Affairs database Duration: October 1999-December 2005.	**n:** 113,272 participants **Baseline characteristics:** **ATN:** N: **346** Age(mean, SD): 63.8 (12.5) **ARF:** N:5058 Age(mean, SD): 66.5 (12.2) **CON:** N:63491 Age(mean, SD): 68.7 (11.9) **CKD:** N:44377 Age(mean, SD): 74.4 (10.6)	**Study type:** Retrospective cohort Inclusion: All patients in the VA decision support system database with at least one inpatient admission with a primary diagnosis of ARF or ATN as markers for an episode of AKI. Patients with PNE or MI codes (ICD9 codes) were designated as controls (CON).	Patients divided into 4 groups: **ATN**: those with at least one ATN admission, but no admissions for MI or PNE **ARF:** those with 1 or more ARF admissions, but no ATN, PNE or MI admissions CON: those with PNE or MI admissions but no ARF or ATN admissions **CKD:** Patients with one of the above admission diagnoses who also had CKD who were removed from the above 3 groups and examined separately. Patients labelled CKD if they entered CKD3,4 or 5 or started chronic dialysis before the first ATN/ARF/MI/PNE admission date and had mean eGFR <60ml/min/1.73m^2.	**ESRD** defined as time from diagnosis to development of CKD4 n developed CKD4/ total (cox regression HR)	ATN: 69/345 (6.64) ARF: 663/5021 (4.03) CON: 2100/62850 (1.0) CKD: 9263/37562 (6.50) TOTAL: 12095/105778	**Source of funding:** Part supported by Satellite Research, Norman S Coplon Extramural Research Grant **Additional info:** Confounders adjusted for: Acute renal failure, acute tubular necrosis, CKD, age, Caucasian, African American, Hispanic, gender, pre-admission diabetes mellitus, diagnosis date, mean pre-admission serum creatinine, mean pre-admission albumin and teaching hospital (y/n).
				Mortality Time from diagnosis to death N died/ total n (cox regression HR)	ATN: 127/345 (1.10) ARF: 1958/5021 (1.12) CON: 24622/62850 (1.00) CKD: 23544/44076 (1.20) TOTAL: 50251/112292	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
		Exclusion:CKD4 or higher before diagnosis date	MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. Date of death from VA BIRLS death file. SC values <0.4 or above 25mg/dl were coded as missing CKD3, 4, and 5 were defined as the first day when eGFR dropped below the threshold after which it never returned above the threshold for that patient Chronic dialysis was defined as having at least 13 outpatient dialysis visits within a 60 day period. AKI assessed by RIFLE criteria			*95% CI for HR not reported, calculated by NCGC for forest plots. Follow-up: 60 months

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
			Patients censored at death or at 60 months after their diagnosis dates. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan.			

ATN, acute tubular necrosis; ARF, acute renal failure; CON, control; PNE, pneumonia; MI, myocardial infarction.

Table 48: LaFrance et al. 2010

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
J.-P. Lafrance, O. Djurdjev, and A. Levin. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrology Dialysis Transplantation 25 (7):2203-2209,	**n:** 6862 participants **Baseline characteristics** **All** N: 6862 Mean age:69.8 (13.3) Mean baseline	**Study type:** Retrospective cohort **Inclusion:** subjects registered as having CKD between November 2002 and November	Provincial CKD registry, including all patients referred to nephrologists or on dialysis therapy in British Columbia Patients followed up until dialysis, kidney transplantation, death, end of study, discharge to family doctor immigration or loss to follow up.	**ESRD** was defined as time to dialysis initiation HR* (95% CI)	**AKI:** 2.33 (2.07, 2.61) **Age (by 10 years):** 0.78 (0.75, 0.81) **Male:** 1.00 (ref) **Female:** 0.76 (0.68, 0.85) **eGFR (by 5ml/min/1.73m^2):** 0.63 (0.60, 0.65) **time in registry**	**Source of funding:** Not stated, but states 'no declarations of interest'. **Additional info:** Confounders adjusted for: sex, age, baseline eGFR and time in registry before cohort entry.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
2010. **Setting:** British Columbia, Canada **Duration**: November 2002-November 2007	eGFR (ml/min/1.73m^2): 23.6 (5.8) Mean follow up time:19.4 (11.1, 32.4) **AKI** N: 3079 Mean age: 68.0 (13.2) Mean baseline eGFR (ml/min/1.73m^2): 23.7 (5.5) Mean follow up time: 22.9 (13.4, 36.3) **No AKI** N: 3783 Mean age: 70.6 (13.4) Mean baseline eGFR (ml/min/1.73m^2): 23.6 (6.0) Mean follow up	2007, had been followed up for at least 6 months and had at least 3 eGFR values (at least 1 value of 30ml/min/1.73m^2) or less **Exclusion:**	MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. AKI defined as decrease in eGFR of at least 25% and of more then 5ml/min/1.73m^2 compared to baseline eGFR. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Cox proportional hazard ratios (RRs) were calculated reference group. These were adjusted for age, sex, baseline eGFR and time in registry before cohort entry. A look back period of 180 days was used for analysis.		**before cohort entry (by year):** 0.84 (0.76, 0.92) **n/total:** AKI: 711/3079 No AKI: 533/3783	*Study states that adjusted relative risks were calculated using a cox-proportional hazard model and Kaplan Meier curves are presented – NCGC assumes these are therefore Hazard ratios. Follow-up: 4 years
				Mortality risk of pre-dialysis mortality HR* (95% CI)	**AKI:** 2.32 (2.04, 2.64) **Age (by 10 years):** 1.87 (1.75, 2.00) **Male**:1.00 (ref) **Female:** 0.75 (0.67, 0.86) **eGFR (by 5ml/min/1.73m^2):** 0.81 (0.76, 0.85) **time in registry before cohort entry (by year):** 1.15 (1.06, 1.26) **n/total:** AKI: 554/3079 No AKI: 492/3783	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	time: 17.0 (9.5, 28.9)					

Table 49: Pannu et al. 2011

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
N. Pannu, M. James, B. R. Hemmelgarn, J. Dong, M. Tonelli, and S. Klarenbach. Modification of outcomes after acute kidney injury by the presence of CKD. Am.J.Kidney Dis. 58 (2):206-213, 2011. **Setting:** Alberta, Canada. Health and Wellness linked with	**n:** 43,008 participants **Baseline characteristics:** **All patients:** N:43008 Age:62.2 (0.1) Comorbid disease (%): MI: 13 Peripheral vascular disease: 5 cerebrovascular disease: 6 Congestive heart failure: 12 Diabetes (%): Uncomplicated: 14 Complicated: 5 **eGFR**	**Study type:** Retrospective cohort **Inclusion:** patients 18 years and older, hospitalised between January 2003 and December 2006, with at least 1 outpatient sCR measurement within 6 months prior to admission. **Exclusion:** Patients with records that indicated treatment with dialysis or kidney transplant before the	Patients stratified into eGFR groups. MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. AKI defined as change between the baseline and highest in-	**ESRD or death** HR (95% CI) [events/total]	**No AKI** **eGFR ≥60:** 1.00 (referent) [823/26357] **eGFR 45-59:** 1.02 (0.94-1.24) [294/5377] **eGFR 30-44:** 1.07 (0.90-1.26) [182/26161] **eGFR <30:** 1.67 (1.34-2.08) [92/802] **AKI Stage 1** **eGFR ≥60:** 2.99 (2.59-3.44) [270/1935] **eGFR 45-59:** 2.92 (2.52-3.40) [234/1358] **eGFR 30-44:** 2.89 (2.50-3.32) [289/1580] **eGFR <30**: 2.93 (2.52-	**Source of funding:** Kidney Foundation of Canada. **Additional info:** Confounders adjusted for: age, sex, comorbid conditions. Mean follow-up not given.

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
laboratory data. **Duration:** January 2003 and December 2006	**≥60:** N: 28,944 Age: 57.3 (0.1) Comorbid disease (%): MI:11 Peripheral vascular disease: 4 cerebrovascular disease:5 Congestive heart failure:6 Diabetes (%): Uncomplicated:13 Complicated:3 **eGFR** **45-59:** N:7023 Age: 72.2 (0.2) Comorbid disease (%): MI: 17 Peripheral vascular disease: 7 cerebrovascular disease: 9 Congestive heart failure: 17 Diabetes (%): Uncomplicated: 19	index hospitalisation were excluded.	hospital SCR value during index hospitalisation. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Cox proportional hazard ratios (HRs) were calculated for ESRD and mortality. These were adjusted for all baseline demographics		3.40) [276/1394] **AKI stage 2** **eGFR ≥60:** 8.28 (6.92-9.92) [143/388] **eGFR 45-59:** 7.53 (5.98-9.47) [85/182] **eGFR 30-44:** 7.46 (5.95-9.35) [88/171] **eGFR <30:** 6.74 (4.96-9.18) [44/108] **AKI stage 3** **eGFR ≥60:** 10.62 (8.78-12.82) [131/264] **eGFR 45-59:** 8.01 (6.12-10.49) [85/182] **eGFR 30-44:** 8.35 (6.20-11.25) [88/171] **eGFR <30:** 4.71 (3.61-6.15) [44/108]	
				Mortality (in hospital) HR (95% CI)	**No AKI** **eGFR ≥60:** 1.00 (referent) [4791/25534] **eGFR 45-59:** 1.02 (0.94, 1.24) [1532/5083]	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Complicated: 6 **eGFR** **30-44:** N: 4460 Age: 75.1 (0.2) Comorbid disease (%): MI:18 Peripheral vascular disease: 9 cerebrovascular disease:9 Congestive heart failure:26 Diabetes (%): Uncomplicated: 18 Complicated: 11 **eGFR** **<30:** N:2581 Age: 71.6 (0.3) Comorbid disease (%): MI: 18 Peripheral vascular disease: 8 cerebrovascular disease:7 Congestive heart				**eGFR 30-44:** 1.07 (0.90, 1.26) [1011/2434] **eGFR <30:** 1.67 (1.34, 2.08) [378/705] **AKI Stage 1** **eGFR ≥60:**2.99 (2.59, 3.44) [495/1665] **eGFR 45-59:** 2.92 (2.52, 3.40) [453/1124] **eGFR 30-44:** 2.89 (2.50, 3.32) [572/1291] **eGFR <30**: 2.93 (2.52, 3.40) [676/1118] **AKI stage 2** **eGFR ≥60:** 8.28 (6.92 (6.92, 9.92) [91/245] **eGFR 45-59:** 7.53 (5.98, 9.47) [46/97] **eGFR 30-44:** 7.46 (5.95, 9.35) [54/83] **eGFR <30:**6.74 (4.96, 9.18) [43/64] **AKI stage 3**	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	failure:28 Diabetes (%): Uncomplicated: 15 Complicated:23				**eGFR ≥60:** 10.62 (8.78, 12.82) [41/133] **eGFR 45-59:** 8.01 (6.12, 10.49) [23/46] **eGFR 30-44:** 8.35 (6.20, 11.25) [26/46] **eGFR <30:** 4.71 (3.61, 6.15) [148/214]	

Table 50: Wu et al. 2011

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
V.-C. Wu, T.-M. Huang, C.-F. Lai, C.-C. Shiao, Y.-F. Lin, T.-S. Chu, P.-C. Wu, C.-T. Chao, J.-Y. Wang, T.-W. Kao, G.-H. Young, P.-R. Tsai, H.-B. Tsai, C.-L. Wang, M.-S. Wu, W.-C. Chiang, I.-J. Tsai, F.-C. Hu, S.-L. Lin, Y.-M. Chen, T.-J. Tsai, W.-J. Ko,	9425 participants **Baseline characteristics (all mean, SD unless otherwise stated)** **Without prior CKD Non-AKI** N:4724 Age: 57.2 (16.8) Comorbidities: -Charlson score:2.8 (4.3)	**Study type:** Prospective cohort **Inclusion:** Admissions to ICU after major surgery. Surgery procedures considered major if length of stay for patients exceeded 2 days.	Patients divided into groups: those without prior CKD, subdivided into AKI risk, Injury and failure; and those with CKD subdivided into non-AKI and AKI. Chinese MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. AKI classified according to	**ESRD** HR (95% CI) [events/total]	**Long term dialysis (subgroups)** Without prior CKD: Non-AKI: 1 (referent) [13/4724] AKI-Risk 2.09 (0.97, 4.52) [14/2434] AKI-Injury: 3.19 (1.27, 8.03) [7/979] AKI-Failure: 22.35 (11.9, 42.1)	**Source of funding:** Te-Tung Kidney Foundation and Taiwan National Science Council (grant) **Additional info:** Confounders adjusted for: age, gender, intervention (extracorporeal membrane oxygenation, ventilator, intra-aortic balloon pump,

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
and K.-D. Wu. Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. Kidney Int. 80 (11):1222-1230, 2011. Setting: Database from National Taiwan University Hospital Study Group **Duration**: January 2002-January 2008	Hypertension:1671 (35.4) Diabetes: 774 (16.4) Liver cirrhosis: 102 (2.2) CHF: 195 (4.1) Chronic hepatitis:134 (2.8) COPD: 145 (3.1) CAD: 1939 (41.1) Atrial fibrillation: 246 (5.2) Cancer: 1941 (41.1) **AKI-Risk** N: 2434 Age (mean, SD): 61.0 (16.7) Comorbidities: -Charlson school: 4.2 (5.2) Hypertension: 949 (39) Diabetes: 533 (21.9) Liver cirrhosis: 151 (6.2)	**Exclusion:** If patients stay in ICU for ≥2 days, repeat ICU admission after index discharge, kidney transplant recipients, patients who died during the hospital admission	sRIFLE criteria, where only serum creatinine for classification. Kidney recovery existed if the discharge sCr remained <50% above baseline sCr. Non-reovery existed if there was a persistent increase in sCr >50% above the baseline sCr or need for dialysis at time of discharge from hospital. Patient survival after discharge was determined through the databank of National Health Insurance Database in January 2009. Cross-linked with Taiwan Society Nephrology Registry. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan.		[58/745] Prior CKD: Non-AKI: 52.0 (25.6, 105.8) [21/2.62] AKI: 122.9 (66.8, 253.9) [69/235] **Renal recovery (n, %) (all subgroups):** Without prior CKD: AKI-risk: 1725 (70.9) AKI-Injury:380 (38.8) AKI- Failure: 164 (22) Prior CKD Non-AKI: - AKI:170 (72.3) Non-recovery (n, %) Without prior CKD:- AKI-risk:709 (29.1) AKI-Injury:599 (61.2) AKI- Failure: 581 (78)	intracranial pressure, transcutaneous pacemaker, Swan-Ganz tube, PiCCO an Sengstaken-Blakemore tube), comorbidity (hypertension, diabetes mellitus, liver cirrhosis, chronic heart failure, chronic hepatitis, COPD, coronary artery disease, atrial fibrillation and cancer) admission subgroups (Charlson score). Follow-up: 6 years

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	CHF: 211 (8.7) Chronic hepatitis: 165 (6.8) COPD: 100 (4.1) CAD: 1062 (43.6) Atrial fibrillation: 195 (8.0) Cancer: 1061 (43.6) **AKI Injury** N:979 Age: 61.7 (16.8) Comorbidities: -Charlson score: 4.6 (5.2) Hypertension:372 (38.0) Diabetes: 234 (23.9) Liver cirrhosis: 83 (8.5) CHF: 147 (15.0) Chronic hepatitis: 95 (9.7) COPD: 48 (4.9) CAD: 393 (40.1)		Cox proportional hazard ratios (HRs) were calculated. These were adjusted for age, sex, admission subgroups, interventions and comorbidity.		Prior CKD Non-AKI:- AKI: 65 (27.7) **Long Term dialysis (without vs.with prior CKD, fewer subgroups)** **Without prior CKD** Non-AKI: 1 (referent) AKI: 4.64 (2.51, 8.56) Prior CKD-non AKI:40.86 (20.01, 83.50) Prior CKD- AKI: 91.6 (49.3, 170.1)	

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Atrial fibrillation: 96 (9.8) Cancer: 395 (40.4) **AKI Failure** N: 745 Age: 60.6 (16.8) Comorbidities: -Charlson score: 4.1 (4.5) Hypertension: 267 (35.8) Diabetes:195 (26.2) Liver cirrhosis: 87 (11.7) CHF: 145 (19.5) Chronic hepatitis: 96 (12.9) COPD: 35 (4.7) CAD: 253 (34.0) Atrial fibrillation: 74 (9.9) Cancer: 243 (32.6) **Prior CKD**					

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	No AKI N: 116 Age: 70.4 (10.7) Comorbidities: -Charlson score: 3.8 (3.5) Hypertension: 78 (67.2) Diabetes:55 (47.4) Liver cirrhosis: 5 (4.3) CHF: 25 (21.6) Chronic hepatitis: 6 (5.2) COPD: 4 (3.5) CAD: 34 (29.3) Atrial fibrillation:6 (5.2) Cancer: 32 (27.6) **CKD-AKI** N: 235 Age: 69.0 (12.5) Comorbidities: -Charlson score: 3.9					

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	(2.8) Hypertension: 132 (56.2) Diabetes: 114 (48.5) Liver cirrhosis: 14 (6.0) CHF: 59 (25.1) Chronic hepatitis: 17 (7.2) COPD: 8 (3.4) CAD: 56 (23.8) Atrial fibrillation: 26 (11.1) Cancer: 49 (20.9) **ESRD** N: 192 Age: 63.2 (12.3) Comorbidities: -Charlson score: 3.0 (2.4) Hypertension: 68 (35.4) Diabetes: 89 (46.4) Liver cirrhosis:12 (6.3) CHF: 34 (17.7)					

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Chronic hepatitis: 14 (7.3) COPD: 4 (2.1) CAD: 46 (25.0) Atrial fibrillation: 19 (9.9) Cancer: 47 (24.5)					

G.5 Frequency of monitoring

Table 51: Amin et al. 2013

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Amin et al.2013[33] Cohort study based on the National Kidney Foundation's Kidney Early	Adults with diabetes and for whom eGFR and albuminuria measurements were available. Median follow up 4 years. Patients, n: 42,761	**Subgroup eGFR 90-104** n= 9158 Age, mean (SD): 55.4 ± 10.0 Male: 33.5% *Ethnicity:* White: 47.3% African American: 28.5% Native American: 4.5%	All-cause mortality (adjusted HR [95% CI])	eGFR ≥ 105	1.00 (reference)	HR adjusted for age, sex, race, insurance status, BMI, education level, family history of diabetes, hypertension, CKD, self
				eGFR 90 - 104	0.84 [0.66-1.06]	
				eGFR 75-89	0.88 [0.70-1.11]	
				eGFR 60-74	0.92 [0.73-1.16]	
				eGFR 45-59	1.23 [0.97-1.56]	
				eGFR 30-44	1.40 [1.09-1.80]	
				eGFR <30	1.74 [1.31-2.31]	
				ACR <30mg/g	1.00 (reference)	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Evaluation Program (KEEP). Country: USA	Subgroups : ACR <30 n= 35,046 ACR 30-300 n=6632 ACR >300 n=1083 eGFR ≥ 105 n= 5714 eGFR 90 – 104 n= 9158 eGFR 75-89 n=10,354 eGFR 60-74 n=8917 eGFR 45-59 n=5383 eGFR 30-44 n=2555 eGFR <30 n=680 Exclusions <18 years old	Asian: 7.6% Other: 12.1% SBP: 134.7 ± 19.0 DBP: 80.0 ± 11.1 *Diabetic Medication:* Yes: 43.8% No: 31.0% Missing: 25.2% *ACR Category:* <30: 86.5% 30-300: 12.4% >300: 1.0% **Subgroup eGFR 75-89** n= 10354 Age, mean (SD): 61.0 ± 11.1 Male: 35.3% *Ethnicity:* White: 53.5% African American: 29.4% Native American: 3.0% Asian: 6.5% Other: 7.6%		ACR 30-300mg/g	1.79 [1.62-1.97]	reported hypertension, measured blood pressure, hypercholestrolaemia, smoking status, haemoglobin level, diabetes medications and insulin use.
				ACR >300mg/g	3.16 [2.70-3.70]	
			Progression to ESRD (adjusted HR [95% CI])	eGFR ≥ 105	1.00 (reference)	
				eGFR 90 - 104	1.51 [0.77-2.93]	
				eGFR 75-89	1.83 [0.97-3.47]	
				eGFR 60-74	2.86 [1.54-5.33]	
				eGFR 45-59	5.93 [3.25-10.80]	
				eGFR 30-44	18.48 [10.27 – 33.22]	
				eGFR <30	84.20 [46.57-152.22]	
				ACR <30mg/g	1.00 (reference)	
				ACR 30-300mg/g	6.44 [4.81-8.61]	
				ACR >300mg/g	15.11 [10.90-20.95]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		SBP: 136.8 ± 19.4 DBP: 79.4 ± 11.4 *Diabetic Medication:* Yes: 46.3% No: 30.2% Missing: 23.5% *ACR Category:* <30: 86.0% 30-300: 12.5% >300: 1.5% **Subgroup eGFR 60-74** n= 8917 Age, mean (SD): 65.2 ± 10.4 Male: 35.7% *Ethnicity:* White: 55.7% African American: 29.6% Native American: 3.1% Asian: 5.2% Other: 6.3% SBP: 137.7 ± 19.4 DBP: 78.3 ± 11.3				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		Diabetic Medication: Yes: 48.0% No: 28.0% Missing: 24.0% *ACR Category:* <30: 83.4% 30-300: 14.7% >300: 1.9% **Subgroup eGFR 45-59** n= 5383 Age, mean (SD): 69.1 ± 10.2 Male: 34.3% *Ethnicity:* White: 61.6% African American: 25.4% Native American: 3.0% Asian: 4.9% Other: 5.2% SBP: 138.1 ± 20.0 DBP: 76.3 ± 11.6 *Diabetic Medication:* Yes: 48.7%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		No: 27.5% Missing: 23.8% *ACR Category:* <30: 76.2% 30-300: 20.2% >300: 3.6% **Subgroup eGFR 30-44** n= 2555 Age, mean (SD): 72.1 ± 9.9 Male: 32.0% *Ethnicity:* White: 62.9% African American: 24.1% Native American: 3.3% Asian: 4.2% Other: 5.4% SBP: 139.3 ± 21.4 DBP: 74.2 ± 12.3 *Diabetic Medication:* Yes: 50.3% No: 25.3% Missing: 24.4%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		ACR Category: <30: 63.8% 30-300: 28.1% >300: 8.1% **Subgroup eGFR <30** n= 680 Age, mean (SD): 69.8 ± 12.6 Male: 38.7% *Ethnicity:* White: 53.8% African American: 29.3% Native American: 3.2% Asian: 6.9% Other: 6.8% SBP: 141.1 ± 23.4 DBP: 74.3 ± 13.5 *Diabetic Medication:* Yes: 41.9% No: 27.8% Missing: 30.3% *ACR Category:* <30: 35.9%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		30-300: 35.4% >300: 28.7% **Subgroup ACR 30-300 mg/g** n= 6632 Age, mean (SD): 61.9 ± 13.8 Male: 38.9% *Ethnicity:* White: 44.7% African American: 33.7% Native American: 4.6% Asian: 6.4% Other: 9.6% SBP: 142.1 ± 21.9 DBP: 80.6 ± 12.8 *Diabetic Medication:* Yes: 48.7% No: 24.2% Missing: 27.1% *eGFR Category:* eGFR ≥ 105: 12.7% eGFR 90 – 104: 17.2%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		eGFR 75-89: 19.5% eGFR 60-74: 19.8% eGFR 45-59: 16.4% eGFR 30-44: 10.8% eGFR <30: 3.6% **Subgroup ACR >300 mg/g** n= 1083 Age, mean (SD): 62.0 ± 13.4 Male: 39.0% *Ethnicity:* White: 44.1% African American: 28.8% Native American: 8.7% Asian: 7.2% Other: 11.2% SBP: 151.2 ± 24.8 DBP: 82.2 ± 13.7 *Diabetic Medication:* Yes: 46.1% No: 22.8% Missing: 31.1% *eGFR Category:*				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		eGFR ≥ 105: 6.3% eGFR 90 – 104: 8.8% eGFR 75-89: 14.5% eGFR 60-74: 15.6% eGFR 45-59: 17.6% eGFR 30-44: 19.2% eGFR <30: 18.0%				

Table 52: Barbour et al. 2010

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Barbour et al. 2010[56] Cohort study on ethnicity based on data from universal health care system. Country: Canada	People from three different ethnic origins (Caucasian, Oriental Asian and South Asian) referred to nephrology with CKD (eGFR <60 and/or evidence of kidney damage from urinalysis or based on biopsy or ultrasound results). Referral to nephrologist Minimum follow up: 2 years Maximum follow up: 8 years Patients, n: 3,444 Subgroups : Caucasian n = 2626	**Caucasian:** Age: 70 [58-78] Male: 59% Diabetes: 42% CVD: 36% eGFR: 27.4 ± 11.9 eGFR 30-60: 38% eGFR 15-30: 48% eGFR <15: 14% Proteinuria: Normal: 27% Moderate: 13% Severe: 17% Not Available: 43% SBP: >130 mmHg: 42% ≤130 mmHg: 25% Not Available: 33% DBP: >80 mmHg: 20% ≤80 mmHg: 47% Not Available: 33%	All-cause mortality (multivariate HR [95% CI]) with RRT as a time-varying covariate	Caucasian Oriental Asian South Asian	1.00 (reference) 0.69 [0.55-0.88] 0.80 [0.63-1.02]	HR adjusted for Age, gender, eGFR, diabetes, CVD, haemoglobin, albumin, calcium, phosphate, iPTH, proteinuria, DBP, ACE inhibitors or ARB, Vitamin D and statin Annualised rate of eGFR progression (mean ± SD, median [IQR] and range) showed South Asian group most likely to progress, followed by Oriental Asian and then Caucasian. Study also reported HR using a competing risk approach.

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
	OA = 397 SA = 421 Exclusions: • Patients who did not identify self-reported race as Caucasian, OA or SA • No presence of CKD • Incomplete data set for multivariate analysis	ACE inhibitors /ARB: 90% Vitamin D: 53% Statin: 58% **Oriental Asian:** Age: 71 [58-78] Male: 53% Diabetes: 40% CVD: 23% eGFR: 25.5 ± 11.9 eGFR 30-60: 35% eGFR 15-30: 44% eGFR <15: 21% Proteinuria: Normal: 16% Moderate: 16% Severe: 35% Not Available: 33% SBP: >130 mmHg: 24% ≤130 mmHg: 17% Not Available: 59%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		DBP: >80 mmHg: 12% ≤80 mmHg: 29% Not Available: 59% ACE inhibitors /ARB: 91% Vitamin D: 55% Statin: 63% **South Asian:** Age: 64 [53-73] Male: 56% Diabetes: 56% CVD: 32% eGFR: 27.9 ± 12.3 eGFR 30-60: 39% eGFR 15-30: 47% eGFR <15: 14% Proteinuria: Normal: 18% Moderate: 15% Severe: 27% Not Available: 40%				

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		SBP: >130 mmHg: 43% ≤130 mmHg: 20% Not Available: 37% DBP: >80 mmHg: 21% ≤80 mmHg: 42% Not Available: 37% ACE inhibitors /ARB: 84% Vitamin D: 42% Statin: 45%				

Table 53: de Goeij et al. 2012

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
de Goeij et al.2012[156] Cohort study based on the	Adults with CKD stage 4 to 5 on predialysis care. Median (IQR) follow	No proteinuria(UPE ≤0.3g/24h) n= 45 Age, median (IQR): 67 (56-75) Diabetes: 4% Systolic blood pressure, mean	Progression to RRT (adjusted HR [95% CI])	No proteinuria	1.00 (reference)	HR adjusted for age, sex, primary kidney disease, systolic blood pressure, haemoglobin
				UPE >0.3 to ≤1.0g/24h	1.70 [1.05-2.77]	
				UPE >1.0 to ≤3.0g/24h	1.87 [1.17-3.00]	
				UPE >3.0 to ≤6.0g/24h	2.62 [1.59-4.33]	
				UPE >6.0g/24h	2.52 [1.45-4.39]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
PREPARE-1 cohort. Country: The Netherlands	up 11.6 (4.7-22.4) months. Patients, n: 413 Exclusions Less than one month on predialysis care or prior RRT	(SD): 150 (27) UPE, median (IQR): 0.2 (0.1-0.3) eGFR, mean (SD): 17.1 (9.2) Proteinuria>0.3 to ≤1.0 n= 88 Age, median (IQR): 67 (52-75) Diabetes: 8% Systolic blood pressure, mean (SD): 144 (25) UPE, median (IQR): 0.6 (0.4-0.8) eGFR, mean (SD): 13.6 (4.6) Proteinuria>1.0 to ≤3.0 n= 132 Age, median (IQR): 66 (48-73) Diabetes: 15% Systolic blood pressure, mean (SD): 152 (26) UPE, median (IQR): 1.9 (1.4-2.5) eGFR, mean (SD): 13.1 (5.6) Proteinuria>3.0 to ≤6.0 n= 101				level, baseline eGFR, cardiovascular disease and diabetes.

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		Age, median (IQR): 54 (44-70) Diabetes: 22% Systolic blood pressure, mean (SD): 160 (29) UPE, median (IQR): 4.0 (3.5-4.4) eGFR, mean (SD): 11.6 (4.2) Proteinuria>6.0 n= 47 Age, median (IQR): 61 (52-70) Diabetes: 49% Systolic blood pressure, mean (SD): 161 (30) UPE, median (IQR): 7.6 (6.9-10.1) eGFR, mean (SD): 11.2 (3.6)				

Table 54: Dreyer et al. 2013

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Dreyer et al. 2013[170] Cohort study on ethnicity based on data from 135 general practices in east London. Country: UK	People from three different ethnic origins (Caucasian, Black African/Caribbean and South Asian) with diabetes and CKD (eGFR 16-60) with no RRT at start of observation period. Minimum follow up: 3 years Maximum follow up: 5 years Patients, n: 3,855 Subgroups :	**Caucasian:** Age: 65 ± 8.1 Male: 61% Mean duration diabetes (years): 7.8±8.6 Hypertension: 78% eGFR: 51.4 Proteinuria:26.5% (Not Available: 30%) ACE inhibitors /ARB: 80% **South Asian:** Age: 63 ± 8.5 Male: 51% Mean duration diabetes (years): 8.8±7.7	CKD progression: change in eGFR	**Whole population**		Annualised rate of eGFR progression (mean ± SD, median [IQR] and range) showed Black African/Caribbean with proteinuria group most likely to progress, followed by South Asian and then Caucasian. Black defined as people of Black African, Black Caribbean, Black British, other black
				Caucasian	-2.66	
				South Asian	-4.25	
				Black African/ Caribbean	-3.13	
				Proteinuria		
				Caucasian	-7.25	
				South Asian	-8.17	
				Black African/ Caribbean	-11.61	
				No proteinuria		
				Caucasian	-1.29	
				South Asian	-2.02	
				Black African/ Caribbean	-0.38	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
	Caucasian n = 1,509 (39.1%) South Asian n = 1,725 (44.7%) Black African/Caribbean n=621 (16.1%) Exclusions: • Age less than 30 or greater than 75 years at entry to study • RRT at entry to study	Hypertension: 74% eGFR: 51.0 Proteinuria: 36% (Not Available: 30%) ACE inhibitors /ARB: 80% **Black African/Caribbean:** Age: 64 ± 8.2 Male: 60% Mean duration diabetes (years): 9.9±8.1 Hypertension: 89% eGFR: 52.5 Proteinuria:30% (Not Available: 27%) ACE inhibitors /ARB: 84%				and mixed black family origin.

Table 55: Hoefield et al. 2010

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Hoefield et al.2010[271] Cohort study based on the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). Single centre. Country: UK	Adults with CKD stage 3-5 not on dialysis therapy. Median follow up 26 months. By protocol eGFR was determined every 12 months. Patients, n: 1325 Subgroups : CKD 3a: 238 (8%) CKD 3b: 431 (33%) CKD 4: 481 (36%) CKD 5: 175 (13%) Exclusions Previous RRT	eGFR 45-59 n= 238 Age, mean (SD): 61.3 (15) Diabetes: 21.4% Cardiovascular disease: 43.3% Proteinuria (g/d): 0.6 (1.27) Ethnicity: 98.3% White eGFR 30-44 n= 431 Age, mean (SD): 65.1 (15) Diabetes: 31.1% Cardiovascular disease: 46.4% Proteinuria (g/d): 0.87 (1.65) Ethnicity: 99.3% White eGFR 15-29 n= 481 Age, mean (SD): 67.0 (14.2) Diabetes: 38.0%	All-cause mortality (adjusted HR [95% CI])	eGFR 45-59	1.00 (reference)	HR adjusted for age, sex, diabetes, smoker, cardiovascular disease, renin-angiotensin blockade, statin, systolic and diastolic blood pressure, haemoglobin, phosphate, PTH, albumin, cholesterol, CRP, proteinuria. Single centre study.
				eGFR 30-44	1.65 [0.98-2.77] P=0.05	
				eGFR 15-29	2.38 [1.43-3.97] P=0.001	
				eGFR <15	2.57 [1.35-4.88] P=0.004	
			Progression to RRT (adjusted HR [95% CI])	eGFR 45-59	1.00 (reference)	
				eGFR 30-44	1.88 [0.62-5.68] P=0.3	
				eGFR 15-29	5.54 [1.96-15.64] P=0.001	
				eGFR <15	18.82 [6.45-54.94] P=<0.001	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
		Cardiovascular disease: 51.1% Proteinuria (g/d): 1.08 (1.86) Ethnicity: 98.5% White eGFR <15 n= 175 Age, mean (SD): 64.8 (13.1) Diabetes: 34.3% Cardiovascular disease: 44.0% Proteinuria (g/d): 2.23 (2.77) Ethnicity: 99.4% White				

Table 56: Levin et al. 2008

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size HR, (95% CI) [n]	
Levin et al. 2008[382] Cohort study using a provincial CKD registry (Patient Registration and Outcomes Management Information System [PROMIS] database) **Country:** Canada	A data set including people with an eGFR less than 30ml/min/1.73m^2 was derived from a registry of all people referred to nephrologists and on dialysis therapy in British Columbia. **Median follow up:** 31 months (range 19-43) **Patients, n:** 4231 **Mean age:** 67 **Male (%):** 64% 33% with diabetes **Race:** 68 % white, 16% Asian oriental, 11% Asian (South/East) 5% other. **Exclusions** People who were deactivated from the	**eGFR < 15 ml/min/1.73m^2** n= 647 Age, mean (SD): 66.8 (14.5) Diabetes: 204 (32%) PCKD/nephropathy/congenital: 103 (20%) Glomerulonephritis (GN)/renal vascular: 157 (31%) Systolic blood pressure, mean (SD) :144.6 (25.7) Diastolic blood pressure, mean (SD): 79.1 (13) Albumin (g/dL) mean (SD): 3.6 (0.52) **eGFR 15-24 ml/min/1.73m^2** n= 1905 Age, mean (SD): 67.8 (14.1)	Renal replacement therapy by eGFR (censored for death) Hazard ratios calculated from Kaplan Meier curves (by NCGC)	eGFR 25-29 * reference group for hazard ratios	[189]	Variables in the analysis include ethnicity, age, sex, medication use, blood pressure, laboratory variables and proteinuria. Comorbid conditions were captured at the time of referral. Cox proportional hazard models were used to identify predictors of mortality before renal replacement therapy (RRT) and predictors of RRT (dialysis initiation or transplantation). Analyses were adjusted for duration of follow-up before
				eGFR 15-24	1.94 (1.73-2.17) [506]	
				eGFR <15	7.52 (6.32-8.49) [343]	
			Mortality before RRT by eGFR level Hazard ratios calculated from Kaplan Meier curves (by NCGC)	eGFR 25-29 * reference group for hazard ratios	[101]	
				eGFR 15-24	1.25 (1.03-1.51) [135]	
				eGFR <15	2.56 (1.87-3.49) [55]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size HR, (95% CI) [n]	
	registry less than 3 months after the index result (n=145) and people with less than 3 eGFR results during a 4-month period (n=520). To ensure cohort represents long-term patients seen in nephrology offices. (i.e. those excluded had an index eGFR on the day they started dialysis therapy or had acute disease but were registered as long term in error).	Diabetes: 656 (34%) PCKD/nephropathy/congenital: 245 (17%) GN/renal vascular: 504 (35%) Systolic blood pressure, mean (SD): 141 (24.9) Diastolic blood pressure, mean (SD): 76.3 (13.3) Albumin (g/dL) mean (SD): 3.7 (0.51) **eGFR 25-29ml/min/1.73m^2** n= 1679 Age, mean (SD): 66.7 (14.8) Diabetes: 547 (33%) PCKD/nephropathy/congenital: 236 (19%) GN/renal vascular: 423 (33%) Systolic blood pressure, mean (SD): 139.8 (23.6) Diastolic blood pressure,				eGFR <30ml/min/1.73m^2 to account for selection bias.

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size HR, (95% CI) [n]	
		mean (SD): 76.9 (12.7) Albumin (g/dL), mean (SD): 3.8 (0.52)				

Table 57: Lorenzo et al. 2010

Study and Country	Population and Exclusions	Baseline characteristics	Outcome	Covariates	Effect size (hazard ratio)	Limitations/ Comments
Lorenzo et al. 2010[399] Retrospective cohort study **Country:** Spain (Canary Islands)	People with CKD (GFR<50ml/min) Mean follow 30 ± 18 months (range 4-79 months). **Participants, n:** data collected from 407. Analysis restricted to 333 who had more than 3 serum creatinine tests to calculate the rate of decline in kidney function. Visits scheduled every 2-4 month, or more often if necessary. All	64% received angiotensin-II receptor enzyme inhibitors or angiotensin-II-receptor antagonists or both as antihypertensive and renoprotective medication. Baseline characteristics were collected from electronic medical records: Age (years): 66.8±14.5 Gender (% male): 63 CV comorbidity (%): 49.5 MDRD (ml/min): 24.7±7.4 ACR (mg/g): 1026 (242-2312) SBP (mm/Hg): 139±15 DBP (mm/HG): 76±9 RAS blockers (%): 63.7 Diabetes (%): 46.0 During follow-up: 1334 initiated dialysis, 26 died, 12 lost to follow-up and 4 received pre-emptive kidney-pancreas transplantation.	**Dialysis-free survival (effect of diabetes)**	Diabetes + age + sex + MDRD (at baseline)	1.83 (1.29:2.58) P<0.001	GFR calculated using the MDRD equation. More than 3 measurements required to estimate the slope. Dialysis-free survival curves estimated by the Kaplan-Meier method – number at risk not reported, so hazard ratios could not be calculated. Multivariate Cox proportional-hazard regression used to assess the relationship of diabetes as independent variable with time to initiation of dialysis (adjusted for age, gender, mean systolic blood pressure, MDRD at entry, baseline cardiovascular comorbidity, BMI, lipid profile, estimated protein intake, smoking status and renin-angiotensin system blocker medication). Linear regression also calculated – not reported here.
				Diabetes + age + sex + MDRD (at baseline) + SBP	1.52 (1.08:2.16) P<0.02	
				Diabetes + age + sex + MDRD (at baseline) + ACR decline	1.3 (0.81:2.10) P=0.279	

Study and Country	Population and Exclusions	Baseline characteristics	Outcome	Covariates	Effect size (hazard ratio)	Limitations/ Comments
	participants received standard care.					

Table 58: Marks et al. 2013

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Marks et al.2013[421] Cohort study based on the Grampian Laboratory Outcomes	Adults with CKD stage 3-4 Follow up 6 years. Patients, n: 3322	**Progressors** (sustained drop of eGFR by 15 or to 10ml/min/1.73m^2) n= 435 Age, median (range): 74.9 (16-97) Male: 250 (57.5%) Type 1 Diabetes: 16 (3.7%)	Progression - sustained drop of eGFR by 15 or to 10ml/min/1.73m^2 (adjusted HR [95% CI])	CKD stage 3	1.00 (reference)	HR adjusted for age, sex, CKD and proteinuria status at baseline. Diabetes not adjusted for in
				CKD Stage 4	0.96 [0.78-1.20]	
				Normoalbuminuria	1.00 (reference)	
				Microalbuminuria (ACR≥2.5mg/mmol for men or ≥3.5mg/mmol for women)	1.70 [1.07-2.68]	
				Macroalbuminuria	3.14 [2.21-4.45]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Morbidity and Mortality Study (GLOMMS-I) Country: UK	Subgroups : CKD 3: 2289 (69%) CKD 4: 1044 (31%) Exclusions: RRT CKD stage 5	Type 2 Diabetes: 106 (24.4%) Hypertension: 245 (56.3%) ACR (mg/mmol), median (range): 15 (0.9-669) eGFR (ml/min/1.73m^2), median (range): 35.1 (15-49) **Non-progressors** n= 2887 Age, median (range): 79.1 (18-103) Male: 1223 (42.4%) Type 1 Diabetes: 40 (1.4%) Type 2 Diabetes: 659 (22.8%) Hypertension:1507 (52.2%) ACR (mg/mmol), median (range): 3 (0.9-858) eGFR (ml/min/1.73m^2), median (range): 33.4 (15-50)		(ACR≥30mg/mmol or PCR ≥50mg/mmol)		model. HRs for comorbidities reported separately. Baseline characteristics only reported for progressors versus non-progressors
			Progression - sustained 25% reduction in eGFR and CKD stage change (adjusted HR [95% CI])	CKD stage 3	1.00 (reference)	
				CKD Stage 4	0.47 [0.36-0.61]	
				Normoalbuminuria	1.00 (reference)	
				Microalbuminuria	1.51 [0.95-2.40]	
				Macroalbuminuria	3.59 [2.54-5.09]	
			Progression to RRT (adjusted HR [95% CI])	CKD Stage 3	1.00 (reference)	
				CKD Stage 4	5.60 [3.84-8.15]	
				Normoalbuminuria	1.00 (reference)	
				Microalbuminuria	2.07 [0.82-5.21]	
				Macroalbuminuria	5.31 [2.86-9.88]	

Table 59: Perkins et al. 2011

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Perkins et al. 2011[539] Cohort study based on data repository of a large integrated healthcare system in central Pennsylvania. Country: USA	Adults aged 18 -88 with non dialysis dependent CKD with an eGFR 15-59 using CKD EPI creatinine equation. Median follow up 3.4 years. Patients, n: 15,465 Exclusions <18 years old >88 years old Any solid organ	Declining eGFR n= 5103 Age, mean (SD): 75.5 (10.8) Diabetes: 1939 (38%) Hypertension: 3674 (72%) Mean eGFR (SD): 49 (9.1) Proteinuria: 526 (31%) Ethnicity: 94.4% White Rate of eGFR change ml/min/yr, median (IQR): -4.8 (-98.2 to -3.2) Stable eGFR n= 5255 Age, mean (SD): 74.4 (9.8) Diabetes: 1627 (31%) Hypertension: 3940 (75%) Mean eGFR (SD): 48 (9.4)	All-cause mortality (adjusted HR [95% CI])	Declining eGFR	2.22 [1.94-2.55]	Cohort stratified by tertile of rate of eGFR change. HR adjusted for age, sex, race, smoking history, hypertension, dementia, chronic liver disease, heart failure, peripheral vascular disease, Charlson Comorbidity Index score, prescription for beta blocker,
				Stable eGFR	1.00 (reference)	
				Increasing eGFR	1.73 [1.50-2.00]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
	transplant Prior haemo- or peritoneal dialysis Metastatic cancer Active prescription for cytotoxic or immunosuppressive therapy. Censoring criteria: ESRD (eGFR <10, RRT) >18 months without serum creatinine result	Proteinuria: 289 (20%) Ethnicity: 95.8% White Rate of eGFR change ml/min/yr, median (IQR): -0.6 (-1.4 to 0.0) Increasing eGFR n= 5107 Age, mean (SD): 72.8 (10.9) Diabetes: 1414 (28%) Hypertension: 3563 (70%) Mean eGFR (SD): 48 (9.4) Proteinuria: 342 (20%) Ethnicity: 95.0% White Rate of eGFR change ml/min/yr, median (IQR): +3.5 (+1.9 to +6.7)				loop diuretic, aldosterone antagonist, calcium acetate, insulin, Coumadin or aspirin, systolic and diastolic blood pressure, proteinuria, serum albumin, HDL and LDL cholesterol, baseline eGFR. Also reported results for model with hospital and/or community acquired acute kidney injury during follow up.

Table 60: Turin et al. 2012 and 2012A

Study and Country	Population and Exclusions	Baseline characteristics	subgroups	Outcomes		Limitations/ Comments
				Outcome measure	Effect size	
Turin et al 2012[685,686] Cohort study based on Alberta Kidney Disease Network data repository. **Country:** Canada	Adults with at least two outpatient CKD-EPI creatinine eGFR measurements (at least 6 months apart) during 1 year accrual period. Minimum follow up 1 year. Median follow up 3.5 years. **Participants, n:** 598,397 **Subgroups (from table A1)*:** eGFR ≥90 n=260,589 eGFR 60-89 n=269,753 eGFR 45-59	**Certain drop** n= 19,591 (3.3%) Age, mean (SD): 63.3 (17.4) Diabetes: 23.4% Hypertension: 57% Mean eGFR (SD): 78.9 (24.1) Proteinuria Normal: 42.0% Mild: 9.9% Heavy: 5.4% Unmeasured:42.8% **Uncertain drop** n= 64,067 (10.7%) Age, mean (SD): 58.6 (15.1) Diabetes: 15.1% Hypertension: 43.6% Mean eGFR (SD): 84.8 (18.7) Proteinuria Normal: 54.4% Mild: 6.4% Heavy: 1.7%	**Certain drop**	ESRD by 1 year change in kidney function (adjusted HR [95% CI])	5.11 [4.56-5.71]	No data on ethnicity available, although <1% of the Alberta population is black. *Population numbers in table A1 appendix (for subgroups) differ from total in rest of study. HR adjusted for age, sex, diabetes, hypertension, socioeconomic status, kidney function, proteinuria, history of
				Baseline eGFR ≥90	4.49 [3.12-6.47]	
				Baseline eGFR 60-89	5.20 [3.94-6.86]	
				Baseline eGFR 45-59	5.57 [4.11-7.55]	
				Baseline eGFR 30-44	4.02 [3.18-5.08]	
				Baseline eGFR 15-29	4.85 [4.01-5.87]	
				All-cause mortality (adjusted HR [95% CI])	1.89 [1.83-1.95]	
				Baseline eGFR ≥90	1.64 [1.51-1.79]	
				Baseline eGFR 60-89	1.85 [1.76-1.93]	
				Baseline eGFR 45-59	1.82 [1.71-1.94]	
				Baseline eGFR 30-44	2.06 [1.90-2.23]	
				Baseline eGFR 15-29	2.07 [1.79-2.39]	
			Uncertain drop	ESRD	2.13 [1.84-2.47]	
				Baseline eGFR ≥90	1.08 [0.72-1.61]	
				Baseline eGFR 60-89	1.96 [1.38-2.80]	
				Baseline eGFR 45-59	1.86 [1.31-2.66]	
				Baseline eGFR 30-44	2.31 [1.73-3.10]	
				Baseline eGFR 15-29	2.93 [2.20-3.91]	

Study and Country	Population and Exclusions	Baseline characteristics	subgroups	Outcomes		Limitations/ Comments
				Outcome measure	Effect size	
	n=50,989 eGFR 30-44 n=20,084 eGFR 15-29 n=5982 **Exclusions:** <18 years old RRT at baseline Baseline eGFR <15ml/min/1.73m^2 ≥24 creatinine measurements in 1 year (possibly indicating unstable kidney function or frequent illness)	Unmeasured: 37.5% **Stable** n= 447,570 (74.8%) Age, mean (SD): 54.6 (17.0) Diabetes: 13.1% Hypertension: 36.5% Mean eGFR (SD): 87.8 (21.4) Proteinuria Normal:57.2% Mild:5.9% Heavy:1.2% Unmeasured: 35.8% **Uncertain rise** n= 44,998 (7.5%) Age, mean (SD): 57.9 (14.8) Diabetes: 13.8% Hypertension: 41.2% Mean eGFR (SD) : 76.4 (15.7) Proteinuria Normal: 56.0% Mild: 6.2% Heavy: 1.1%		All-cause mortality	0.98 [0.95-1.01]	cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, myocardial infarction, liver disease, paralysis, peptic ulcer disease, peripheral vascular disease and rheumatic disease at time of first measurement. Results adjusted for covariates at the last measurement also reported.
				Baseline eGFR ≥90	0.72 [0.68-0.76]	
				Baseline eGFR 60-89	0.99 [0.96-1.04]	
				Baseline eGFR 45-59	1.22 [1.15-1.30]	
				Baseline eGFR 30-44	1.24 [1.13-1.36]	
				Baseline eGFR 15-29	1.64 [1.29-2.08]	
			Stable	ESRD/ All-cause mortality	1.00 (reference)	
				Reference group for hazard ratios		
			Uncertain rise	ESRD	0.39 [0.30-0.51]	
				Baseline eGFR ≥90	Not applicable	
				Baseline eGFR 60-89	0.38 [0.21-0.68]	
				Baseline eGFR 45-59	0.65 [0.39-1.06]	
				Baseline eGFR 30-44	0.42 [0.26-0.70]	
				Baseline eGFR 15-29	0.25 [0.15-0.43]	
				All-cause mortality	1.12 [1.08 -1.16]	
				Baseline eGFR ≥90	Not applicable	
				Baseline eGFR 60-89	1.81 [1.72-1.92]	
				Baseline eGFR 45-59	0.98 [0.93-1.04]	
				Baseline eGFR 30-44	0.84 [0.78-0.91]	
				Baseline eGFR 15-29	0.85 [0.74-0.97]	
			Certain rise	ESRD	0.33 [0.26-0.42]	

Study and Country	Population and Exclusions	Baseline characteristics	subgroups	Outcomes		Limitations/ Comments
				Outcome measure	Effect size	
		Unmeasured:36.7% Certain rise n= 22,171 (3.7%) Age, mean (SD): 59.9 (17.8) Diabetes: 16.3% Hypertension: 48.6% Mean eGFR (SD): 59.6 (17.8) Proteinuria Normal: 48.3% Mild: 8.7% Heavy: 2.1% Unmeasured: 41.0%		Baseline eGFR ≥90	Not applicable	
				Baseline eGFR 60-89	0.63 [0.32-1.25]	
				Baseline eGFR 45-59	0.58 [0.34-0.98]	
				Baseline eGFR 30-44	0.35 [0.23-0.55]	
				Baseline eGFR 15-29	0.18 [0.12-0.27]	
				All-cause mortality	1.51 [1.46-1.56]	
				Baseline eGFR ≥90	Not applicable	
				Baseline eGFR 60-89	4.29 [3.97-4.63]	
				Baseline eGFR 45-59	1.55 [1.46-1.64]	
				Baseline eGFR 30-44	1.21 [1.13-1.29]	
				Baseline eGFR 15-29	0.93 [0.85-1.02]	

Table 61: Van Pottelbergh et al. 2012

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
Van Pottelbergh et al. 2012[696] Cohort study based on data from Intego, a Flemish general practice-based morbidity registration network. Country: Belgium	Adults aged ≥50 years with ≥4 serum creatinine measurements. GFR estimated by MDRD. Mean follow up 7.8 years (SD 3.90). Patients, n: 24,682 Subgroups : Baseline eGFR >60 n= 19,931 Baseline eGFR 45-60 n=3748 Baseline eGFR 30-45 n=840 Baseline eGFR 15-30 n=162 Exclusions:	Age, mean (SD): 64 (NR) Diabetes: 18% Hypertension: 62% Proteinuria: NR Ethnicity: NR	Progression to ESRD (adjusted HR [95% CI])	Age 50 – 64 (n=14160)	1.00 (reference)	HR adjusted for diabetes, hypertension, high total cholesterol, high LDL cholesterol and gender.
				Age 65-79 (n=8743)		
				Baseline eGFR >60	2.49 [2.41-2.57]	
				Baseline eGFR 45-60	2.78 [2.61-2.94]	
				Baseline eGFR 30-45	0.70 [0.62-0.78]	
				Baseline eGFR 15-30	0.58 [0.41-0.75]	
				Age 80+ (n=1779)		
				Baseline eGFR >60	4.43 [4.03-4.83]	
				Baseline eGFR 45-60	2.55 [2.15-2.95]	
				Baseline eGFR 30-45	0.52 [0.43-0.61]	
				Baseline eGFR 15-30	0.30 [0.23-0.37]	

Study and Country	Population and Exclusions	Baseline characteristics	Outcomes			Limitations/ Comments
			Outcome measure	Subgroups	Effect size	
	<50 years old eGFR <15 "People with impossible serum creatinine values".					

G.6 Progression of CKD after acute kidney injury

Table 62: Amdur et al. 2009

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Richard L. Amdur, Lakhmir S. Chawla, Susan Amodeo, Paul L. Kimmel, and Carlos E. Palant. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 76 (10):1089-	**n:** 113,272 participants **Baseline characteristics:** **ATN:** N: **346** Age(mean, SD): 63.8 (12.5) **ARF:** N:5058	**Study type:** Retrospective cohort Inclusion: All patients in the VA decision support system database with at least one inpatient admission with a	Patients divided into 4 groups: **ATN**: those with at least one ATN admission, but no admissions for MI or PNE **ARF:** those with 1 or more ARF admissions, but no ATN, PNE or MI admissions CON: those with PNE or MI admissions but no ARF or ATN admissions **CKD:** Patients with one of the	**ESRD** defined as time from diagnosis to development of CKD4 n developed CKD4/ total (cox regression HR)	ATN: 69/345 (6.64) ARF: 663/5021 (4.03) CON: 2100/62850 (1.0) CKD: 9263/37562 (6.50) TOTAL: 12095/105778	**Source of funding:** Part supported by Satellite Research, Norman S Coplon Extramural Research Grant **Additional info:** Confounders adjusted for: Acute renal failure, acute tubular necrosis, CKD,

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
1097, 2009. **Setting:** United States Department of Veterans Affairs database Duration: October 1999-December 2005.	Age(mean, SD): 66.5 (12.2) **CON:** N:63491 Age(mean, SD): 68.7 (11.9) **CKD:** N:44377 Age(mean, SD): 74.4 (10.6)	primary diagnosis of ARF or ATN as markers for an episode of AKI. Patients with PNE or MI codes (ICD9 codes) were designated as controls (CON). **Exclusion:**CKD4 or higher before diagnosis date	above admission diagnoses who also had CKD who were removed from the above 3 groups and examined separately. Patients labelled CKD if they entered CKD3,4 or 5 or started chronic dialysis before the first ATN/ARF/MI/PNE admission date and had mean eGFR <60ml/min/1.73m^2. MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. Date of death from VA BIRLS death file. SC values <0.4 or above 25mg/dl were coded as missing CKD3, 4, and 5 were defined as the first day when eGFR dropped below the threshold after which it never returned above the			age, Caucasian, African American, Hispanic, gender, pre-admission diabetes mellitus, diagnosis date, mean pre-admission serum creatinine, mean pre-admission albumin and teaching hospital (y/n). *95% CI for HR not reported, calculated by NCGC for forest plots. Follow-up: 60 months

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
			threshold for that patient Chronic dialysis was defined as having at least 13 outpatient dialysis visits within a 60 day period. AKI assessed by RIFLE criteria Patients censored at death or at 60 months after their diagnosis dates. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan.			

ATN, acute tubular necrosis; ARF, acute renal failure; CON, control; PNE, pneumonia; MI, myocardial infarction.

Table 63: Hsu et al. 2009

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
C. Y. Hsu, G. M. Chertow, C. E. McCulloch, D.	39,805 participants with CKD; 1061had superimposed **dialysis-requiring acute renal failure** during	**Study type:** Retrospective cohort	**ARF**: peak inpatient serum	**ESRD** (defined as the	**ARF**: Of the 213 survivors (no ESRD or death within 30	**Source of funding:** National Institute of Diabetes and Digestive

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
Fan, J. D. Ordonez, and A. S. Go. Nonrecovery of kidney function and death after acute on chronic renal failure. Clin.J.Am.Soc.Nephrol. 4 (5):891-898, 2009.	hospitalisation (ARF group) and 38,744 did not (no ARF group). **Baseline characteristics:** Mean age: ARF group: 66.6 (13.5); no ARF: 73.5 (12.9) years % women: ARF: 460 (43.4%); no ARF: 22.915 (59.1%) White/ European: ARF: 611 (57.6%); no ARF: 28,570 (73.7%) Black/African American: ARF: 156 (14.7%), no ARF: 2923 (7.5%) Hispanic: ARF: 104 (9.8%), no ARF: 1856 (4.8%) Asian/ Pacific Islander: ARF: 117 (11.0%), no ARF: 2987 (7.7%) Native American: ARF: 10 (0.9%), no ARF: 288 (0.7%) Mixed/ unknown: ARF: 63 (5.9%), no ARF: 2120 (5.5%) Diabetes: ARF: 614 (57.9%). no ARF: 10,517 (27.1%) Hypertension: ARF: 864 (81.4%), no ARF: 26,993 (69.7%) Proteinuria: ARF: 749 (70.6%), no ARF: 11,475 (29.6%)	**Inclusion:** Adults aged 20 years or older hospitalised between Jan 1st 1996 and Dec 31st 2003 who were Kaiser Permanente members and had one or more outpatient determination of serum creatinine giving an eGFR <45ml/min/1.73m^2 (MDRD equation); first hospitalisation per person during study period only. **Exclusion:** Patients with previous kidney transplant or on maintenance dialysis	creatinine > last outpatient value by ≥50% plus acute dialysis **Statistical analysis:** Proportion of patients who died during index admission. Proportion of hospital survivors with ESRD within 30 days of discharge. Cox proportional hazard ratios (HRs) adjusted for age, gender, race,	start of renal replacement therapy [dialysis or transplant]) in survivors within 6 months of discharge. Adjusted HR (95% CI)	days), 12.7% developed ESRD within 6 months. **No ARF**: Of the 34,721 survivors (no ESRD or death within 30 days), 1.7% developed ESRD within 6 months. HR 1.47 (0.95 to 2.28) (reference group no ARF)	and Kidney Diseases. **Confounders adjusted for:** Age, gender, race/ethnicity, preadmission eGFR, diabetes, diagnosed hypertension, known proteinuria

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	CHD: ARF: 532 (50.1%), no ARF: 10,622 (27.4%) Stroke/TIA: ARF: 273 (25.7%), no ARF: 6728 (17.4%) Peripheral artery disease: ARF: 363 (34.2%), no ARF: 5045 (13.0%) Chronic heart failure: ARF: 603 (56.8%), no ARF: 8414 (21.7%) Dyslipidaemia: ARF: 576 (54.3%), no ARF: 13,602 (35.1%) Chronic lung disease: ARF: 399 (37.6%), no ARF: 10,059 (26.0%) Chronic liver disease: ARF: 45 (4.2%), no ARF: 816 (2.1%) Cancer: ARF: 165 (15.6%), no ARF: 6010 (15.5%) Hypoalbuminaemia: ARF: 628 (59.2%), no ARF: 4990 (12.9%) Dementia: ARF: 31 (2.9%), no ARF: 2447 (6.3%) Serum creatinine: ARF: 3.31 (1.67) mg/dL; no ARF: 2.11 (1.42) eGFR 30–44 ml/min/1.73m^2: ARF: 294 (27.7%), no ARF: 28,434 (73.4%) 15–19 ml/min/1.73m^2: ARF: 476		pre-admission eGFR and co-morbid conditions.			

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	(44.9%), no ARF: 7763 (20.0%) <15 ml/min/1.73m^2: ARF: 291 (27.4%), no ARF: 2547 (6.6%)					

Table 64: Ishani et al 2009

Reference	No. of patients & characteristics	Inclusion/ exclusion criteria	Intervention	Outcome measures	Effect sizes	Source of funding/ Comments

Reference	No. of patients & characteristics	Inclusion/ exclusion criteria	Intervention	Outcome measures	Effect sizes	Source of funding/ Comments
Ishani A et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009; 20: 223-228. **Study type:** Retrospective cohort Follow-up: 2 years	233,803 patients ≥67 years on discharge. Of those discharged alive: Mean age 79.2 years Male 38.8% White: 89.0% Black: 7.7% Other: 3.3% Diabetes: 27.2% Hypertension: 64.9% Heart disease: 69.3% CKD: 3.1% AKI 3.1%, of whom prior CKD in 34.3% Overall prior CKD: 12%	**Inclusion**: Hospitalised in 2000 with discharge diagnosis of AKI from 5% random sample of Medicare beneficiary claims data; age ≥67 years at hospital discharge; Medicare 2 years prior to hospitalisation; survived hospital admission; no history of ESRD before hospital discharge; no previous AKI in 2 years prior to current event **Exclusion**: AKI and died in hospital People who recovered kidney function within 180 days of ESRD initiation were classified as non-ESRD.	AKI (n=7197, of whom 2467 also had CKD) No AKI (n=226,606, of whom 25,653 had CKD)	**ESRD** (defined as enrolment in the ESRD program) HR (95% CI)	Overall: 5.3/1000 developed ESRD; of those discharged with AKI, 25.2% had ESRD AKI and CKD: HR: 41.2 (34.6 to 49.1) (reference group no AKI or CKD) AKI without previous CKD: HR: 13.0 (10.6 to 16.0) (reference group no AKI or CKD) HR for AKI total (with or without CKD): 6.74 (5.90 to 7.71) (reference group no AKI).	National Institute of Diabetes and Digestive and Kidney Diseases. Cox proportional hazards models adjusted for age, gender, race, diabetes, hypertension.

Table 65: James et al. 2010A

Reference	No. of patients and characteristics	Inclusion/ exclusion criteria	Intervention	Outcome measures	Effect sizes	Source of funding/ Comments
James MT et al. Glomerular filtration rate, proteinuria, and the incidence and consequence of acute kidney injury: a cohort study. Lancet 2010; 376: 2096–103. **Study type:** Retrospective cohort **Follow-up:** Median 35 months	920,985 patients **Inclusion:** Age ≥18 years; with at least 1 outpatient measurement of serum creatinine and one of proteinuria in Alberta, Canada, between 2002 and 2007. **Exclusion:** ESRD at baseline (eGFR <15ml/min/1.73m^2, chronic dialysis or kidney transplant)	Baseline eGFR (n): ≥60ml/min/1.73 m^2: 820,571 45–59.9 ml/min/1.73m^2: 79,845 30–44.9 ml/min/1.73m^2: 16,713 15–29.9 ml/min/1.73m^2: 3856.	AKI (n=6520)broken down by severity (eGFR and proteinuria levels) No AKI, normal proteinuria and eGFR≥60ml/ min/1.73m^2	ESRD or doubling of serum creatinine HR for patients with AKI (95% CI); referent group for all HR = no AKI, normal proteinuria and eGFR≥60ml/ min/1.73m^2	eGFR ≥60ml/min/1.73m^2: Proteinuria normal (urine dipstick negative): 30 (24–37) Proteinuria mild (urine dipstick trace or 1+): 39 (29–52) Proteinuria heavy (urine dipstick 2+): 107 (77–150) eGFR 45–59.9 ml/min/1.73m^2: Proteinuria normal: 21 (16–27) Proteinuria mild: 23 (16–32) Proteinuria heavy: 87 (62–122) eGFR 30–44.9 ml/min/1.73m^2: Proteinuria normal: 24 (18–32) Proteinuria mild: 33 (24–45) Proteinuria heavy: 80 (58–110) eGFR 15–29.9 ml/min/1.73m^2: Proteinuria normal: 50 (36–70) Proteinuria mild: 76 (54–108) Proteinuria heavy: 230 (165–320)	Alberta Heritage Foundation for Medical Research Poisson regression models adjusted for: age, sex, aboriginal status, low income, social assistance and comorbidities. Kaplan Meier plots not shown.

Table 66: James et al. 2011B

Reference	No. of patients and characteristics	Inclusion/ exclusion criteria	Intervention	Outcome measures	Effect sizes	Source of funding/ Comments
James MT et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 2011; 123: 409–416. **Study type:** Retrospective **Follow-up:** Median 19.7 months	14,782 patients AKI defined using AKIN criteria. Mean age no AKI : 62.6 years; mild AKI 68.0 years; moderate/ severe AKI 67.4 years Male: no AKI : 71.6%; mild AKI 70.9%; moderate/ severe AKI 67.6% Mean eGFR before angiography: no AKI: 75.3ml/min/ 1.73m^2; mild AKI: 66.6 ml/min/ 1.73m^2; moderate/ severe AKI: 58.5 3ml/min/ 1.73m$^{2.}$	**Inclusion:** Patients undergoing coronary angiography in Alberta, Canada from 1 January 2004 to 31 December 2006; ≥18 years; at least 1 serum creatinine measurement from 6 months prior to angiography and another measurement within 7 days after. **Exclusion:** Renal transplant or dialysis before angiography; no serum creatinine measurement prior to or within 7 days after angiography.	AKI: AKIN 1 or AKIN 2-3 No AKI	ESRD HR (95% CI) defined as initiation of chronic RRT.	AKIN 1: HR 4.15 (2.32 to 7.42) AKIN 2-3: HR 11.74 (6.38 to 21.59) Reference: no AKI Event rates for ESRD: No AKI 29/21864 AKIN 1: 25/1610 AKIN 2-3: 39/339	Kidney Foundation of Canada and Alberta Kidney Disease Network Covariates: age, sex, baseline eGFR and proteinuria, comorbidities, coronary revascularisation (PCI or CABG), coronary anatomy and left ventricular ejection fraction

Table 67: Jones et al. 2012

Reference	No. of patients and characteristics	Inclusion/ exclusion criteria	Intervention	Outcome measures	Effect sizes	Source of funding/ Comments
Jones J et al. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis 2012; 60: 402–408. **Study type:** Retrospective cohort study **Follow-up:** Median 2.5 years	3809 patients Mean age 58 (18) years Male: 48% AKI stage I (serum creatinine increased 50–100%): n=224 AKI stage II (serum creatinine increased 100–200%): n=261 AKI stage III (serum creatinine increased >200%): n=234	**Inclusion:** Adult patients with at least 1 hospitalisation between January 1, 1999 and December 31, 2009 with clinical data at least 90 days prior to admission and at least 1 serum creatinine; plus data at least 1 year after admission **Exclusion:** <18 years; pregnant; outpatient or inpatient diagnosis of ESRD; inpatient dialysis; prior diagnosis of AKI or eGFR <60ml/min/1.73m^2	AKI by ICD-9 definition (n=719): complete recovery of kidney function at discharge (serum creatinine level within 7 days of discharge to <1.10 times baseline). No AKI (n=3090).	Incident CKD stage 3 (eGFR <60ml/min/1.73m^2) Adjusted HR (95% CI)	AKI: 108/719 (15%) and no AKI: 97/3090 (3%) HR 3.82 (2.81 to 5.19)	American Heart Association, Genzyme Nephrology Fellowship Award, National Institute of Diabetes and Digestive and Kidney Disease Logistic regression model to calculate propensity score analysis; covariates: age, sex, race, comorbidity, hypertension, prior inpatient visits, admission day, baseline serum creatinine

Table 68: LaFrance et al. 2010

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
J.-P. Lafrance, O. Djurdjev, and A. Levin. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrology Dialysis Transplantation 25 (7):2203-2209, 2010. **Setting:** British Columbia, Canada **Duration**: November 2002-November 2007	**n:** 6862 participants **Baseline characteristics** **All** N: 6862 Mean age:69.8 (13.3) Mean baseline eGFR (ml/min/1.73m^2): 23.6 (5.8) Mean follow up time:19.4 (11.1, 32.4) **AKI** N: 3079 Mean age: 68.0 (13.2) Mean baseline eGFR (ml/min/1.73m^2): 23.7 (5.5) Mean follow up time: 22.9 (13.4, 36.3) **No AKI** N: 3783 Mean age: 70.6 (13.4) Mean baseline eGFR (ml/min/1.73m^2): 23.6 (6.0)	**Study type:** Retrospective cohort **Inclusion:** subjects registered as having CKD between November 2002 and November 2007, had been followed up for at least 6 months and had at least 3 eGFR values (at least 1 value of 30ml/min/1.73m^2) or less	Provincial CKD registry, including all patients referred to nephrologists or on dialysis therapy in British Columbia Patients followed up until dialysis, kidney transplantation, death, end of study, discharge to family doctor immigration or loss to follow up. MDRD equation was used to estimate GFR from age, sex, ethnic origin and serum creatinine concentration. AKI defined as a decrease in eGFR of at least 25% and of more then 5ml/min/1.73m^2 compared to baseline	**ESRD** was defined as dialysis initiation HR* (95% CI)	**AKI:** 2.33 (2.07, 2.61) **n/total:** AKI: 711/3079 No AKI: 533/3783	**Source of funding:** Not stated, but states 'no declarations of interest'. **Additional info:** Confounders adjusted for: sex, age, baseline eGFR and time in registry before cohort entry. *Study states that adjusted relative risks were calculated using a cox-proportional hazard model and Kaplan Meier curves are presented – NCGC assumes these are therefore Hazard ratios. Follow-up: 4 years

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Intervention	Outcome measures	Effect sizes	Comments
	Mean follow up time: 17.0 (9.5, 28.9)		eGFR. **Statistical analysis:** Investigators from each study analysed their data in accordance with an a priori analytical plan. Cox proportional hazard ratios (RRs) were calculated reference group. These were adjusted for age, sex, baseline eGFR and time in registry before cohort entry. A look back period of 180 days was used for analysis.			

Table 69: Lo et al. 2009

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
Lo LL et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney International 2009; 76: 893–899. **Study type:** Retrospective cohort study **Follow-up:** 10,344 person-years or follow up	3773 patients Mean age ARF: 62.3 (15.3) years; matched controls 62.6 (15.5) years Male: 62% White: 66.5% Black: 11.7% Hispanic: 7.9% Asian/Pacific Islander: 7.3% Other: 6.7%	**Inclusion:** Members of Kaiser Permanente of Northern California; age ≥20 years; hospitalised between 1 January 1996 and 31 December 2003 with serum creatinine before hospitalisation giving eGFR ≥45ml/min/1.73m^2 by MDRD equation **Exclusion:** ESRD before admission	Dialysis-requiring ARF (peak inpatient serum creatinine ≥50% higher than baseline and renal replacement therapy during admission); survived admission; did not develop ESRD within 30 days of discharge (n=343) No ARF (n=3430)	Progressive CKD (eGFR ≤30ml/min/1.73 m^2 or ESRD) Adjusted HR (95% CI)	ARF: 47.9 per 100 person-years; no ARF: 1.7 per 100 person-years HR 28.1 (21.1 to 37.6)	National Institutes for Health Each patient matched to 10 controls on baseline eGFR, diabetes, age, sex, race/ethnicity. Cox proportional hazards model.

Table 70: Newsome et al. 2008

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
Newsome BB et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 2008; 168: 609–616. **Study type:** Retrospective cohort **Follow-up:** Median 4.1 years	87,094 patients Mean age 77.1 (7.5) years Male 50% African American: 7.0% White: 93.0% **Baseline sCr µmol/l (SD) :** Decrease/no change in sCr: 115 (62) Quartile 1: 106 (44) Quartile 2: 106 (44) Quartile 3: 115 (62) Quartile 4: 150	**Inclusion:** Medicare beneficiaries admitted with acute myocardial infarction between February 1994 and July 1994 **Exclusion:** Long-term renal replacement in hospital or death in hospital; ESRD before admission; transfer in or out (within 24 hours) of the index hospital; race not African American or white; age <65 years; acute haemodialysis during hospitalisation; patients in 99th percentile of increase in serum creatinine during hospitalisation; missing data.	Increase in serum creatinine level during admission. Decrease or no change in serum creatinine level during admission.	ESRD Adjusted HR (95% CI where shown in text; other CIs shown on graph only, all significantly different from reference group)	Quartile 1: increase 0.1mg/dL (9µmol/l): HR 1.45 quartile 2: increase 0.2mg/dL (18µmol/l): HR 1.97; quartile 3: 0.3 to 0.5 mg/dL (27-44µmol/l): 2.36; quartile 4: 0.6 to 3.0mg/dL (53-265µmol/l): 3.26 (2.73 to 3.71). NOTE: Quartiles 1 and 2 show a small rise in serum creatinine but would not be defined as AKI.	Funding: none reported Cox proportional hazards model adjusted for demographic characteristics (age, sex, race), comorbidity (history of stroke, hypertension, diabetes, previous myocardial infarction or coronary bypass, smoking), reduced kidney function on admission, anaemia on admission. sCr converted from mg/dL to µmol/l (multiplied by 88.4)

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
	(88)					95% confidence intervals calculated from lower 95% confidence interval read from graph and upper 95% confidence interval calculated by NCGC using RevMan 5.2, asymmetrical confidence intervals shown in graph. For the one group reported in the text only the lower 95% interval agrees with that shown in the graph.

Table 71: Thakar et al. 2011

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
Thakar C et al. Acute kidney injury episodes and chronic	3679 patients: 1822 hospitalised, of whom 530 had AKI, 1292 hospitalised no AKI, 1857	**Inclusion:** Patients with diabetes seeking care in VA healthcare system	AKI during each hospitalisation: 0.3mg/dL (27µmol/l) or 1.5-	Development of stage 4 CKD (GFR <30ml/	Effect of up to 3 episodes of AKI versus hospitalised no AKI: HR 2.02 per episode (1.78 to	Veterans Health Administration

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
kidney disease risk in diabetes mellitus. CJASN 2011; 6: 2567-2572. **Study type:** Retrospective cohort. **Follow-up:** Mean 61.2 (25) months	not hospitalised Mean age 61.7 (11.2%) Male: 97.7% Black: 18.8% Other: 81.2% Baseline GFR: 81.1 (25.9) ml/min/1.73m^2 Baseline creatinine: 1.10 (0.3) mg/dL	between January 1, 1999 and December 31, 2004 **Exclusion:** <3 outpatient creatinine values, eGFR <30 ml/min/1.73m^2	fold increase in creatinine relative to admission level for that hospitalisation. No AKI	min/1.73m^2) HR (95% CI)	2.30) Effect of up to 3 episodes of AKI versus hospitalised no AKI by baseline GFR: GFR <60ml/min/1.73m^2: HR 1.61 (1.28 to 2.03); GFR 60 to 90ml/min/1.73m^2: 2.33 (1.93 to 2.81); GFR >90ml/min/1.73m^2: 2.27 (1.69 to 3.06)	Cox regression analysis; covariates: demographic variables, baseline creatinine; chronic comorbid conditions

Table 72: Wald et al 2009

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
Wald R et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009; 302:	17,367 patients Mean age 62 years Male: 60%	**Inclusion:** Adults (≥19 years) with AKI requiring dialysis, admitted to acute care hospital between July 1, 1996 and December 31, 2006; length of stay <180 days,	AKI requiring dialysis (n=3769) Controls: patients without AKI or dialysis during hospitalisation matched (1–4 per case)	Chronic dialysis beginning >30 days after discharge and lasting ≥90 days	HR 3.23 (2.70 to 3.86) (reference group no AKI) No prior CKD: HR 15.54 (9.65 to 25.03) (Prior CKD figures only	Ontario Ministry of Health and Long-Term Care and University of Toronto Faculty of Medicine

Reference	Number of patients & characteristics	Inclusion / exclusion criteria	Risk factor	Outcome measures	Effect sizes	Source of funding/ Comments
1179–1185. **Study type:** Retrospective cohort **Follow-up:** Median 3 years	Charlson comorbidity index: 2.7 CKD in prior 5 years: 25%	surviving 30 days free of dialysis or re-hospitalisation after discharge. **Exclusion:** AKI, kidney transplant or dialysis in previous 5 years; no matches found in dataset.	on age, sex, CKD in previous 5 years, ventilation during admission and propensity score for developing AKI requiring dialysis (n=13,598)		shown graphically)	Cox proportional hazards models adjusted for age and propensity score

G.7 Low protein diet

Table 73: Brouhard 1990

Study	Brouhard 1990[94]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=15)
Countries and setting	Conducted in USA; Setting: Outpatient
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Microalbuminuria of at least 30 µg/minute
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Brouhard 1990[94]
Inclusion criteria	Background or proliferative retinopathy; serum creatinine at or below 8mg/dl
Exclusion criteria	Blood pressure greater than 140/90 mmHg in the 3 months before the start of the study
Age, gender and ethnicity	Age - Mean (SD): Intervention: 36 (13); Control: 30 (12). Gender (M:F): 9:6. Ethnicity: Not reported
Further population details	1. Older people aged 75 years and over: Not applicable / Not stated / Unclear 2. People with diabetes: CKD and diabetes
Extra comments	Patients with insulin dependent diabetes mellitus and diabetic nephropathy (microalbuminuria of at least 30 µg/minute)
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day. Duration 12 months. Concurrent medication/care: Blood pressure medications other than angiotensin-converting enzyme inhibitors were adjusted to maintain blood pressure at or below 140/90mmHg (n=7) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). dose/quantity, brand name, extra details. Duration 12 months. Concurrent medication/care: Blood pressure medications other than angiotensin-converting enzyme inhibitors were adjusted to maintain blood pressure at or below 140/90mmHg.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum - Actual outcome: eGFR final values at 12 months; Group 1: mean 71 ml/minute/1.73m^2 (SD 21); n=8, Group 2: mean 47 ml/minute/1.73m^2 (SD 21); n=7; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Compliance (measured by actual protein intake) (Important) at 1 year minimum ; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum;

Study	Brouhard 1990[94]
	Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 74: Cianciaruso 2008, Cianciaruso 2008

Study (subsidiary papers)	Cianciaruso 2008[127] (Cianciaruso 2009[126])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=423 randomised)
Countries and setting	Conducted in Italy; Setting: CKD clinic of university hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR obtained with the MDRD equation
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years and over with a basal value of eGFR less than or equal to 30ml/min/1.73m^2
Exclusion criteria	Unstable renal function, malignant diesase, treatment with immunosuppressant drugs, urinary protein excretion exceeding 5g/24h, pregnancy or refusal to participate.
Recruitment/selection of patients	Consecutive patients were screened for inclusion criteria and randomly assiged to one of two test diets. Randomisation was generated by a computer. eGFR checked monthly for 3 months (baseline) if stable (eGFR variability <15%) people were deemed eligible for the study.
Age, gender and ethnicity	Age - Mean (SD): 61 (18). Gender (M:F): --Define--. Ethnicity: Not stated
Further population details	1. Older people aged 75 years and over: Not applicable / Not stated / Unclear (Age range not stated). 2. People with diabetes: Not applicable / Not stated / Unclear (Mixed).
Extra comments	Aged 18 years with CKD and stable kidney function. Baseline eGFR (ml/min/1.73m^2): low protein diet 16 +/- 6, higher

Study (subsidiary papers)	Cianciaruso 2008[127] (Cianciaruso 2009[126])
	protein diet 17 +/- 8 Stage 4/5: low protein diet 106/94, higher protein diet 92/100.
Indirectness of population	No indirectness
Interventions	(n=212) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). Target low protein diet was 0.55g/kg/day, but achieved level was 0.71g/kg/day. Duration 18 months. Concurrent medication/care: All dietary prescriptions and estimates of dietary intake are expressed according to the patients' desirable body weight (DBW), derived from the BMI. Patients were prescribed at least 30kcal/kg/day, reduced to a minimum of 25 in overweight patients, or if hypertension and hyperlipidaemia were present. A multivitamin and mieral tablet was also administered daily. Dietary sodum intake was restricted in all patients (2.5g/day of sodium). Calcium supplements were given in the form of calcium carbonate in order to guarantee a calcium intake of 100-1500mg/day. Iron supplementation was administered as necessary to maintain transferrin saturation at 20% or greater, and serum ferritin level at 60 microgram/l. The therapy consisted of 200mg/day of oral element iron. (n=211) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). Target higher protein diet was 0.8g/kg/day, but achieved value was 0.86g/kg/day. Duration 18 months. Concurrent medication/care: As with low protein diet
Funding	Academic or government funding (Partially funded by an unrestricted grant from the Italian Ministry of Univerity and Scientific Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG)

Protocol outcome 1: Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum
- Actual outcome: Progression of CKD (ESRD/RRT) at 48 months; HR 0.98 (95%CI 0.64 to 1.51) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum
- Actual outcome: Progression of CKD (eGFR) at 48 months; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 3: Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum

Study (subsidiary papers)	Cianciaruso 2008[127] (Cianciaruso 2009[126])
- Actual outcome: All-cause mortality at 48 months; HR 1.04 (95%CI 0.59 to 1.83) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Compliance (actual protein intake) at 18 months; Group 1: mean 0.71 g/kg/day (SD 0.12); n=200, Group 2: mean 0.86 g/kg/day (SD 0.05); n=192; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 75: Ciarambino 2012

Study	Ciarambino 2012[128]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 30 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 2 diabetes for at least 15 years treated with diet + insulin; arterial hypertension treated with diet + RAS inhibitors; chronic renal disease stage 3 or 4; >65 years; functionally independent (except on max of 1 of 6 ADL); MMSE >24; no severe disease influencing mood state; Cumulative Illness Rating Scale <3
Exclusion criteria	Thyroid abnormalities or altered B12 and folic acid levels; on antidepressants
Recruitment/selection of patients	Not stated

Study	Ciarambino 2012[128]
Age, gender and ethnicity	Age - Other: Inclusion criterion: >65 years; no mean stated. Gender (M:F): 18:20. Ethnicity: Not stated
Further population details	1. Older people aged 75 years and over: 2. People with diabetes: CKD and diabetes (All had CKD stage 3 or 4 + type 2 diabetes).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). Low protein diet 0.7g/kg 7 days a week. Duration 30 months. Concurrent medication/care: Insulin + RAS inhibitors (n=19) Intervention 2: Low protein diet - Low protein diet (0.6 - 0.8g/kg). Low protein diet 6 days a week plus normal protein diet once a week. Duration 30 months. Concurrent medication/care: Insulin + RAS inhibitors
Funding	Academic or government funding (Italian Regional Founds)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus LOW PROTEIN DIET (0.6 - 0.8G/KG) Protocol outcome 1: Quality of life (Critical) at 1 year minimum - Actual outcome: SF-36 MCS at 30 months; Group 1: mean 36.8 (SD 0.5); n=19, Group 2: mean 49 (SD 0.6); n=19; SF-36 mental component score 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: SF-36 PCS at 30 months; Group 1: mean 37 (SD 0.8); n=19, Group 2: mean 48 (SD 0.9); n=19; SF-36 Physical component score 0-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Nutritional status (measured by change in BMI) (Important) at 1 year minimum - Actual outcome: BMI at 30 months; Group 1: mean 29.7 kg/m^2 (SD 0.5); n=19, Group 2: mean 29.2 kg/m^2 (SD 0.6); n=19; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Compliance (measured by actual protein intake) (Important) at 1 year minimum ; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Progression of CKD

Study	Ciarambino 2012[128]
	(measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum

Table 76: Klahr 1994, Levey 2006

Study (subsidiary papers)	Klahr 1994[344] (Levey 2006[380])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=585)
Countries and setting	Conducted in USA; Setting: Multicentre trial (15 clinical centres)
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GFR assessed by urinary clearane of iothalamate
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Usual vs.low blood presure
Inclusion criteria	Aged 18 - 70; increased serum creatinine, men: 1.4 to 7.0 mg/dl, women 1.2 to 7.0 mg/dl, or other objective evidence of kidney disease; mean arterial blood pressure less than or equal to 125mm Hg; GRF 13-55 ml/min/1.73m^2; urinary protein excretion <10g/day; protein intake >0.9g/kg/day if GFR 25-55 ml/min/1.73m^2.
Exclusion criteria	Insulin-dependent diabetes or fasting serum glucose >200 mg/dl; on dialysis; kidney transplant recipient; lactating or pregnant women or women planning to become pregnant with the time frame of the study; doubtful compliance; body weight <80% or >160% of standard body weight; serum albumin <3 g/dl; selected renal disorders: upper or lower urinary tract obstruction, renal artery stenosis, branched or staghorn calculi, cystinuria; serious medical conditions: malignancy (excluding skin cancer) within 1 year, heart failuer (New York Heart Association class 3 or 4), lung disease, liver disease, gastrointestinal disease, chronic systemic infections including AIDS, collagen vascular disease (other than rheumatoid arthritis), frequent hospitalisations or disability; drugs: immunosuppressive agents, corticosteroids n

Study (subsidiary papers)	Klahr 1994[344] (Levey 2006[380])
	excess of replacement dosage for 2 months peryear or more, gold or penicillamine with past month, salicylates (more than 20 tablets per week), other nonsteroidal antiinflammatory agents more than 3 times per week in past 2 months, investigational drugs; allergy to iothalamate or iodine; inability or unwillingness to give consent.
Recruitment/selection of patients	Selection was conducted in two phases: a screening period for initirial determination of eligibility and a 3-month baseline period. The baseline period was used to intstruct patients about study procedures; to assess GFR and dietary protein intake and to control blood pressure according to standard medical practice. GFR, dietary protein and urinary protein must meet eligibility criteria at the end of the baseline period before an individual can be randomised.
Age, gender and ethnicity	Age - Mean (SD): Low protein diet: 51.8 (12.1), Usual protein diet 25.5 (12.2). Gender (M:F): 61.05% M. Ethnicity: 8% African American
Further population details	1. Older people aged 75 years and over: Aged under 75 (All participants 18 - 70 years old). 2. People with diabetes: CKD only
Extra comments	Adults aged 18 - 70 with chronic kidney disease. . GFR at baseline (ml/min/1.73m^2): low protein diet 39.3 +/- 9, higher protein diet 37.9 +/- 8.8
Indirectness of population	Serious indirectness: Blood pressure also modified
Interventions	(n=250) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). Target value 0.58g/kg. Duration 3 years. Concurrent medication/care: Dietary sodium intake was not restricted. Pharmacologic and nonpharmacologic therapies used to achieve the desired blood-p[ressure values. The recommended antihypertensive regimen was an angiotensin-converting-enzyme inhibitor with or without a diuretic agent; a calcium-channel blocker and other medications were added as needed. Hyperphosphatemia was treated with calcium carbonate as needed. (n=263) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). Target value 1.3g/kg. Duration 3 years. Concurrent medication/care: As with low protein diet
Funding	Academic or government funding (National Institue of Diabetes, Digestive and Kidney Dieases, and the Health Care Finance Administration. Carizem and Oscal provided by Marion Merrell DOw and Vasotec provided by Merck Sharp and Dohme.)

Study (subsidiary papers)	Klahr 1994[344] (Levey 2006[380])
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum - Actual outcome: Progression of CKD (ESRD RRT) at 11 years; HR 0.89 (95%CI 0.71 to 1.12) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum - Actual outcome: Progression of CKD (eGFR) at 3 years; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness Protocol outcome 3: Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum - Actual outcome: Mortality (all cause) at 3 years; Group 1: 5/291, Group 2: 10/294; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Mortality (all cause) at 11 years; Group 1: 63/291, Group 2: 66/294; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Compliance at 3 years; Group 1: mean 0.77 g/kg/day (SD 0.12); n=286, Group 2: mean 1.11 g/kg/day (SD 0.14); n=292; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 77: Locatelli 1991

Study	Locatelli 1991[396]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=456)
Countries and setting	Conducted in Afghanistan, Italy; Setting: Outpatient departments (multicentre)
Line of therapy	Adjunctive to current care

Study	Locatelli 1991[396]
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Creatinine levels used for diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Plasma creatinine concentrations between 133 micromol/l (119 in women) and 619 micromol/l and a creatine clearance rate below 60ml/min.
Exclusion criteria	A variation in plasma creatinine of more than 100% during the 3-month preliminary observation period; diabetes; nephrotic syndrome (defined as proteinuria of more than 3g/24 h and serum albumin below 25 g/l); acute obstructions of the urinary tract; an ideal body weight below 45kg or above 90kg; acute infectious diseases (including those of the urinary tract); systemic illnesses (such as autoimmune or malignant disorders); any other disorder necessitating treatment with drugs that might affect the progression of the underlying renal disease; and previous surgery of the gastrointestinal tract.
Age, gender and ethnicity	Age - Mean (range): 48.5 (18 - 65). Gender (M:F): 247:209. Ethnicity: Italian
Further population details	1. Older people aged 75 years and over: Aged under 75 2. People with diabetes: CKD only
Extra comments	Outpatients aged 18 - 65 with Chronic renal insufficiency. Population stratified into 3 groups: group A plasma creatinine 133-221 micromol/l; group B 222-442 micromol/l; and group C 443-619 micromol/l.
Indirectness of population	--
Interventions	(n=230) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg ideal body weight plus energy supplememnt of 35 kcal/kg daily.. Duration 2 years. Concurrent medication/care: Daily phosphate intake restricted to 0.26 mmol/kg. Patients with hypertension received the following stepped treatment: beta blockers or central antihypertensive agents; calcium channel blockers or other vasodilators; and frusemide. Angiotensin-converting enzyme inhibitors and minoxidil were avoided as much as possible, and vitamin D was not permitted. Calcium carbonate was recommended between meals, to maintain total plasma calcium concentrations at 2.25-2.75 mmol/l; when necessary, calcium carbonate or aluminium hydroxide was given with meals to maintain normal plasma phosphate concentrations. Severe hyperuricaemia was treated with allopuriol; uricosuric agents were not allowed. For treatment of metabolic acidosis, calcium carbonate was supported by the administation of the lowest possible

Study	Locatelli 1991[396]
	doses of sodium bicarbonate. (n=226) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). 1.0g protein per kg daily plus energy supplement of 30 kcal/kg daily. Duration 2 years. Concurrent medication/care: Daily phosphate intake restricted to 0.42 mmol/kg. other treatments as for low protein diet.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum - Actual outcome: Progression of CKD (ESRD RRT) at 2 years; Risk of bias: Low; Indirectness of outcome: -- Protocol outcome 2: Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum - Actual outcome: Mortality (all cause) at 2 years; Group 1: 2/230, Group 2: 3/226; Risk of bias: Low; Indirectness of outcome: -- Protocol outcome 3: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Compliance at 2 years; Other: Low protein diet: 19.7, higher protein diet: -0.1; Risk of bias: Low; Indirectness of outcome: --	
Protocol outcomes not reported by the study	Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 78: Meloni 2002

Study	Meloni 2002[446]
Study type	RCT (Patient randomised; Parallel)

Study	Meloni 2002[446]
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in Italy; Setting: Outpatients
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with overt diabetic nephropathy (not defined); Type 1 or type 2 diabetes traeted with insuin; hypertension treated with ACE inhibitor and calcium blocker therapy with a treated blood pressure of less than or equal to 140/85mmHg for at least 3 months prior to entry
Exclusion criteria	Clinical or biochemical signs of malnutrition
Age, gender and ethnicity	Age - Mean (SD): 54.4 (15.3). Gender (M:F): 38:31. Ethnicity: Not stated
Further population details	1. Older people aged 75 years and over: Aged under 75 (Age range 35-73 years). 2. People with diabetes: CKD and diabetes
Extra comments	Adults with type 1 or type 2 diabetes and overt diabetic nephropathy and hypertension. Baseline eGFR intervention: 45.6 (5.4) ml/min/1.73m^2, control: 44.0 (6.1) ml/min/1.73m^2. None
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day. Duration 12 months. Concurrent medication/care: Insulin and antihypertensives, same for both groups (n=34) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). free-protein diet (mean 1.39g/kg/day). Duration 12 months. Concurrent medication/care: Insulin and antihypertensives, same for both groups
Funding	Funding not stated

Study	Meloni 2002[446]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum - Actual outcome: Change in GFR at 12 months; Group 1: mean 6.15 ml/min/1.73m^2 (SD 1.61); n=35, Group 2: mean 6.26 ml/min/1.73m^2 (SD 1.84); n=34; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Actual protein intake at 12 months; Group 1: mean 0.68 g/kg/day (SD 0.4); n=35, Group 2: mean 1.38 g/kg/day (SD 0.3); n=34; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Nutritional status (measured by change in BMI) (Important) at 1 year minimum - Actual outcome: Obesity index at 12 months; Group 1: mean 10.3 kg (SD 1.6); n=35, Group 2: mean 13.7 kg (SD 2.6); n=34; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 79: Meloni 2004

Study	Meloni 2004[447]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=169)
Countries and setting	Conducted in Italy; Setting: Outpatients
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months

Study	Meloni 2004[447]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	CKD; chronic hypertension treated with both an ACE inhibitor and calcium blocker
Exclusion criteria	Biochemical signs of malnutrition; other systemic disease; chronic infection; malignancy; steroids or immunosuppressive drugs
Age, gender and ethnicity	Age - Mean (SD): 62.2 (13.4). Gender (M:F): 45:44. Ethnicity: Not reported
Further population details	1. Older people aged 75 years and over: Aged under 75 (Age range 29-73 years). 2. People with diabetes: CKD only (Subgroup with CKD and diabetes were excluded (see comments)).
Extra comments	Non diabetic adults with CKD. Different low protein diets for diabetic and non-diabetic subgroups, diabetic subgroup excluded as actual protein intake was 0.9g/kg/day.
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day. Duration 12 months. Concurrent medication/care: None Comments: Home visits to improve compliance if necessary (n=45) Intervention 2: Higher protein diet - Higher protein diet (unrestricted or free protein). Free protein diet (mean 1.54g/kg/day). Duration 12 months. Concurrent medication/care: None
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (UNRESTRICTED OR FREE PROTEIN)

Protocol outcome 1: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum
- Actual outcome: GFR final values at 12 months; Group 1: mean 41.8 ml/min/1.73m^2 (SD 2.4); n=44, Group 2: mean 38.3 ml/min/1.73m^2 (SD 3.8); n=45; Risk of bias:

Study	Meloni 2004[447]
Low; Indirectness of outcome: No indirectness Protocol outcome 2: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Actual protein intake from diet questionnaire at 12 months; Group 1: mean 0.67 g/kg/day (SD 0.21); n=44, Group 2: mean 1.54 g/kg/day (SD 0.39); n=45; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Nutritional status (measured by change in BMI) (Important) at 1 year minimum - Actual outcome: BMI at 12 months; Group 1: mean 23.9 kg/m^2 (SD 2.9); n=44, Group 2: mean 25.1 kg/m^2 (SD 3.4); n=45; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 80: Rosman 1989

Study	Rosman 1989[587]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Switzerland; Setting: Nephrology outpatient department
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 48 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Creatinine clearance 10-60ml/min (how this was measured is not reported)

Study	Rosman 1989[587]
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	CKD (CrCl 10-60ml/min)
Exclusion criteria	Lupus erythematosus; active vasculitis; Wegener's disease.
Recruitment/selection of patients	Patients with CrCl of 31-60 were randomised to either low [protein diet 0.6g/kg/day or usual diet.
Age, gender and ethnicity	Age - Median (range): 48 (15-73) NOTE: this is for all patients, includes 0.4g/kg/day subgroup and their controls that did not meet our inclusion criteria). Gender (M:F): 84:67. Ethnicity: Not reported
Further population details	1. Older people aged 75 years and over: Aged under 75 (All patients under 75 years of age.). 2. People with diabetes: CKD and diabetes (Total number of people with diabetes unclear but <15%.).
Extra comments	CKD (mixed with and without diabetes, although <15% had diabetes). Patients were stratified pre-randomisation for sex, age (above and below 40 years) and renal function (CrCl above and below 30ml/min). Otherwise baseline characteristics not clearly reported by subgroup but states "not statistically different".
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day. Duration 4 years. Concurrent medication/care: Every 3 months visited nephrology and dietician. Compliance measured by urea excretion (actual values not reported). (n=77) Intervention 2: Higher protein diet - Higher protein diet (unrestricted or free protein). "Usual" diet. Duration 4 years. Concurrent medication/care: Nephrology visit every 3 months. Saw dietician "only for a specific indication". Unclear if compliance was measured in this group.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (UNRESTRICTED OR FREE PROTEIN)	

Study	Rosman 1989[587]
Protocol outcome 1: Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum - Actual outcome: Mortality at 4 years; Group 1: 4/74, Group 2: 10/77; Risk of bias: Low; Indirectness of outcome: Serious indirectness - Actual outcome: Progression of CKD (measured by end stage renal disease requiring RRT) at 4 years; Group 1: 7/74, Group 2: 3/77; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Compliance (measured by actual protein intake) (Important) at 1 year minimum ; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 81: Williams 1991

Study	Williams 1991[722]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=65)
Countries and setting	Conducted in United Kingdom; Setting: Nephrology clinical at the Royal Liverpool Hospital or at South Cleveland Hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: mean of 19 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Creatinine clearance
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	--Define--
Exclusion criteria	--Define--
Recruitment/selection of patients	All patients attending the two participating clinics meeting inclusion criteria were eligible. All eligible patients were

Study	Williams 1991[722]
	reviewed on at least 3 occasions over a 6 month period before randomisation. A full clinical assessment, including measurement of height, weight, triceps and subscapuilar skin fold thickness and mid-upper arm circumference. Serum albumin, transferrin and immunoglobulins and 24 hour urine protein excretion were measured. Blood pressure was measured on 3 occasions. Hypertension controlled with most suitable agent for the individual: no particular drug or group of drugs were excluded. Target blood pressure was <150/95 mmHG for patients under 50 years and <170/95 for those over 50 years. Deterioration of renal function was confirmed on the basis of at least 3 measurements of plasma creatinine and 24 hour creatinine clearance over the 6 month period beofer randomisation Patients with uncontrolled acidosis, untreated urinary tract infection or disturbance of salt and water balance were treated conventionally and were stable at randomisation.
Age, gender and ethnicity	Age - Mean (SD): low protein diet: 43 (2.3), usual protein diet: 44.5 (2.2). Gender (M:F): --Define--. Ethnicity:
Further population details	1. Older people aged 75 years and over: Aged under 75 2. People with diabetes: Not applicable / Not stated / Unclear
Extra comments	Adult patients with chnoic renal failure. Plasma creatnine at randomisation: low protein diet, 382 +/- 33 micromol/l, 382 +/-28 micromol/litre
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day . Duration 19 months. Concurrent medication/care: 800mg phosphate, energy intake at least 30 kCal/kg/day (n=32) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). Minimum of 0.8g/kg/day protein. Duration 19 months. Concurrent medication/care: Energy intake at least 30 kCal/kg/day. No phosphate restriction
Funding	Academic or government funding (Mersey Region Association for Kidney Research)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum - Actual outcome: Mortality (all cause) at 24 months; Group 1: 1/31, Group 2: 1/29; Risk of bias: Low; Indirectness of outcome: No indirectness	

Study	Williams 1991[722]
- Actual outcome: Progression of CKD (ESRD RRT) at 24 months; Group 1: 17/31, Group 2: 15/29; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum - Actual outcome: Compliance at Mean of 19 months; Group 1: mean 0.69 g/kg/day (SD 0.11); n=31, Group 2: mean 1.14 g/kg/day (SD 0.27); n=29; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum; Compliance (measured by actual protein intake) (Important) at 1 year minimum ; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum; Quality of life (Critical) at 1 year minimum

Table 82: Zeller 1991

Study	Zeller 1991[739]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=35)
Countries and setting	Conducted in USA; Setting: Outpatients
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean 35 months (minimum12 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Renal function measured by iothalamate clearance at baseline
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 1 diabetes mellitus with onset before the age of 30; diabetic nephropathy (24h protein excretion more than 500 mg); diabetic retinopathy; absence of other causes of renal failure.
Exclusion criteria	Contraindications to a low-protein diet such as severe infection, cancer, pregnancy, history of brittle diabetes, age

Study	Zeller 1991[739]
	under 18 or over 60.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 33 (2); Control: 35 (2). Gender (M:F): 21:14. Ethnicity: Not reported
Further population details	1. Older people aged 75 years and over: Aged under 75 (Aged 18-60). 2. People with diabetes: CKD and diabetes
Extra comments	Mean duration of diabetes: Intervention 21 years. Control 22 years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Low protein diet - Low protein diet (0.6 - 0.8g/kg). 0.6g/kg/day. . Duration Mean 37 months (minimum 12 months). Concurrent medication/care: Diet also contained phosphorus 500-1000mg, sodium 2000mg and calcium 1000mg (supplemented with calcium carbonate). Standard multivitamin preparation. (n=15) Intervention 2: Higher protein diet - Higher protein diet (greater than 0.8g/kg). Greater than or equal to 1g/kg/day. Duration Mean 31 months (minimum 12 months). Concurrent medication/care: Diet also contained sodium 2000mg and at least 1000mg of phosphorus. Standard multivitamin preparation.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PROTEIN DIET (0.6 - 0.8G/KG) versus HIGHER PROTEIN DIET (GREATER THAN 0.8G/KG) Protocol outcome 1: Progression of CKD (measured by change in GFR) (Critical) at 1 year minimum - Actual outcome: GFR (iothalamate clearance) at Mean 35 months; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 2: Compliance (measured by actual protein intake) (Important) at 1 year minimum - Actual outcome: Actual protein intake (calculated from urinary excretion of urea nitrogen) at Mean 37 months; Group 1: mean 0.72 g/kg/day (SD 0.06); n=20, Group 2: mean 1.08 g/kg/day (SD 0.1); n=13; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by end stage renal disease requiring RRT) (Critical) at 1 year minimum; Mortality (all-cause and cardiovascular) (Critical) at 1 year minimum; Nutritional status (measured by subjective global assessment) (Important) at 1 year minimum; Nutritional status (measured by change in BMI) (Important) at 1 year minimum;

Study	Zeller 1991[739]
	Quality of life (Critical) at 1 year minimum

G.8 Self-management

Study	Barrett 2011[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=474)
Countries and setting	Conducted in Canada; Setting: Community (only 4% receiving nephrology care)
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 742 days (614 to 854 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Documented CKD; eGFR 25 to 60 ml/min/1.73m2
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 40 to 75 yrs and had documented CKD with an estimated GFR (eGFR) between 25 and 60 ml/min/1.73m2
Exclusion criteria	Likely to die within 6 months; recently unstable/advanced cardiovascular disease, current treatment for malignancy; receiving immunotherapy for kidney disease; on dialysis or with an organ transplant either currently or within 6 months; already enrolled in a disease management program for kidney disease or cardiovascular disease or another interventional clinical trial; or resident of a location too distant to attend study visits
Recruitment/selection of patients	Patients with elevated serum creatinine levels identified by community laboratories, and their family physicians were then asked to consider referring the patient to the study.
Age, gender and ethnicity	Age - Median (IQR): Intervention: 67 (62, 72); control: 67 (61, 72). Gender (M:F): 211:263. Ethnicity: 94% Caucasian
Further population details	1. Older people aged 75 or over: 2. People from BME gps: 3. People with diabetes:
Indirectness of population	No indirectness
Interventions	(n=238) Intervention 1: Self management support system. Nurse-coordinated care focusing on risk factor

	modification. The nurse followed medical protocols and worked in close collaboration with a nephrologist. Additional clinical care delivered by a study nurse and nephrologist guided by protocols aimed at achieving the prespecified targets but focused on the needs of the individual. Most intervention-group patients were seen for additional interim study visits to address identified clinical issues. There was emphasis on patient self-management and working collaboratively.. Duration Median 742 days (614 to 854 days). Concurrent medication/care: Plus usual care. This meant care delivered by a family doctor providing assessments and treatments for their parents as they saw fit. The family doctors could consult specialists or involve allied health personnel if necessary. (n=236) Intervention 2: Usual care. This means care delivered by a family doctor providing assessments and treatments for their parents as they saw fit. The family doctors could consult specialists or involve allied health personnel if necessary.. Duration Median 742 days (614 to 854 days). Concurrent medication/care: Not stated
Funding	Other (Canadian Institutes for Health Research, Kidney Foundation of Canada, Heart and Stroke Foundation of Canada, Canadian Diabetes Association; Amgen Canada, Ortho Biotech, Merck Frosst Canada)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT SUPPORT SYSTEM versus USUAL CARE Protocol outcome 1: Mortality (all cause and cardiovascular) (Critical) at At stated in paper - Actual outcome: All cause death at 24 months ; Group 1: 7/238, Group 2: 2/236; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Cardiovascular death at 24 months ; Group 1: 2/238, Group 2: 2/236; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at At stated in paper - Actual outcome: Dialysis at 24 months ; Group 1: 2/238, Group 2: 1/236; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (change in eGFR) (Important) at At stated in paper - Actual outcome: Progression of CKD (eGFR declined by 4ml/min/1.73m2 or more) at 20 months of follow-up; Group 1: 28/165, Group 2: 23/165; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation (Important) at At stated in paper; Adherence to treatment at At stated in paper; Outpatient attendance at At stated in paper; Health related quality of life (Important) at At stated in paper

Study	Chen 2011[115]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in Taiwan; Setting: Nephrology outpatient dept
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 1 yr
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: National Kidney Federation classification
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Incidental CKD (stages III-V), an age 18-80 yrs and the ability to communicate in Taiwanese and Mandarin
Exclusion criteria	Cardiovascular disease in the last 3 mths, infections requiring admission in the previous 3 mths, uncontrolled hypertension, serum albumin level > 2.5 g/dL
Age, gender and ethnicity	Age - Mean (SD): Self management 67.93 (12.87) Control 68.39 (12.08). Gender (M:F): 15:12 for both gps. Ethnicity: Taiwanese
Further population details	1. Older people aged 75 or over: Mixed (18-80 yrs). 2. People from BME gps: People from BME gps (Taiwanese). 3. People with diabetes: People with diabetes (>50% diabetes).
Extra comments	Incidental predialysis CKD patients 2008. Education 70% junior high school, hypertension 56%. eGFR ml/min 1.73 m-2 25 (SD13.93), CKD status III 35%, IV 28%, V 37%
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Usual care. Care from a nephrologist. Instructed patients regarding renal function, evaluation of lab data and clinical indicators of chronic renal failure as well as strategies for its management and treatment. Duration 12 mths. Concurrent medication/care: None stated (n=27) Intervention 2: Self management support system. Provision of information, reinforced learning incentives and encouraged self care and maintainenance of the therapeutic regimen. Support from MDT including nurses, dieticians, peers and volunteers. Program included the provision of health information, patient education, telephone-based

	support and the aid of a support group. Individualised lectures of range of topics e.g., renal health. Patient education monthyl one-to-one face-to-face meetings. Support gp twice a month. Biannual dietary counselling. Duration 12 months. Concurrent medication/care: None stated
Funding	Academic or government funding (Chang Gung Memorial Hospital)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT SUPPORT SYSTEM versus USUAL CARE Protocol outcome 1: Mortality (all cause and cardiovascular) (Critical) at At stated in paper - Actual outcome: No hospitalised at 12 mths; Group 1: 5/27, Group 2: 12/27; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Mortality (all cause) at 12 mths; Group 1: 0/27, Group 2: 1/27; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (change in eGFR) (Important) at At stated in paper - Actual outcome: Final eGFR at 12 mths; Group 1: mean 29.11 ml/min 1.73 m-2 (SD 20.61); n=27, Group 2: mean 15.72 ml/min 1.73 m-2 (SD 10.67); n=27; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at At stated in paper; Hospitalisation (Important) at At stated in paper; Adherence to treatment at At stated in paper; Outpatient attendance at At stated in paper; Health related quality of life (Important) at At stated in paper

Study	Mukoro 2012[460]
Study type	Non randomised study
Number of studies (number of participants)	1 (n=365)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 71% used it for >1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Two-thirds of respondents have had a form of renal replacement therapy (RRT), including kidney transplantation (45%), haemodialysis (13%) and peritoneal dialysis (8%). Nearly all participants who were not RRT patients reported having functioning kidneys, although 3% were in conservative care pathway.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: More than 70% of respondents were 26 to 65 yrs, with the majority (39%) in the 51 to 65 yr age gp. . Gender (M:F): 60:40. Ethnicity: 87% British White
Further population details	1. Older people aged 75 or over: 2. People from BME gps: 3. People with diabetes:
Extra comments	Some patient were on dialysis
Indirectness of population	No indirectness
Interventions	(n=365) Intervention 1: Self management support system. Renal Patient View: Secure internet based system that enables kidney patients to view their live test results online and obtain information about their kidney disease. . Duration >1 year. Concurrent medication/care: Not stated
Funding	--

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT SUPPORT SYSTEM [INTERVENTION 1] ONLY Protocol outcome 1: Health related quality of life (Important) at At stated in paper - Actual outcome: Makes me feel more in control of my medical care (strongly agree or agree) at >1 year; Group 1: 226/257, Risk of bias: --; Indirectness of outcome: No indirectness - Actual outcome: Gives me better understanding of my renal disease (strongly agree or agree) at >1 year; Group 1: 229/257, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: Helps me communicate better with my doctor (strongly agree or agree) at >1 year; Group 1: 203/257, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: Helps me to be more involved in decisions about my care (strongly agree or agree) at >1 year; Group 1: 193/257, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: Reassures me about my treatment (strongly agree or agree) at >1 year; Group 1: 198/257, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: The forum is a good place for learning from others (strongly agree or agree) at >1 year; Group 1: 63/103, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: The forum has helped me to learn about symptom(s) I experienced (strongly agree or agree) at >1 year; Group 1: 46/103, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: The forum is helping me cope better with problems in my life (strongly agree or agree) at >1 year; Group 1: 33/103, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: The forum is a good place of social support (strongly agree or agree) at >1 year; Group 1: 49/103, Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: The forum has helped me to find ways of reducing treatment side effects (strongly agree or agree) at >1 year; Group 1: 28/103, Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at At stated in paper; Progression of CKD (change in eGFR) (Important) at At stated in paper; Hospitalisation (Important) at At stated in paper; Adherence to treatment at At stated in paper; Outpatient attendance at At stated in paper; Mortality (all cause and cardiovascular) (Critical) at At stated in paper

Study	Williams 2012[720]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Australia; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 mths
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: urine microalbumin/creatinine ratios 2-6020 mg/mmol
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People age ≥ 18 yrs of age who comprehended English, who were mentally competent, who had Type 1 or Type 2 diabetes and CKD estimated by a Modified Diet in Renal Disease eGFR > 15 (≤ 60 ml/min/1.73m²) or diabetic kidney disease (microalbumin/creatinine rations > 2.0 mg/mmol for men, > 3.5 mg/mmol for women), a systolic hypertension ≥ 130 mmHg treated with prescribed hypertensive medication
Exclusion criteria	If they lived more than 50 km from the city centre, were pregnant or had received a new diagnosis of cancer
Age, gender and ethnicity	Age - Mean (SD): intervention 68 (8.3) control 66 (10.8). Gender (M:F): Intervention and control 56%. Ethnicity: Country of birth Australia 36%
Further population details	1. Older people aged 75 or over: Mixed 2. People from BME gps: Not applicable / Not stated / Unclear 3. People with diabetes: People with diabetes
Extra comments	Note: n=1389 assessed for eligibility
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Self management support system. Self monitoring of blood pressureIndividualised medication review20 min Digital Versatile Disc (DVD)Fortnightly motivational interviewing follow-up telephone contact For 12 wks to support blood pressure control and optimal medication self-managementDelivered by an intervention nurse with renal specialist and doctoral qualifications trained in motivational interviewing. Duration 3 mths. Concurrent medication/care: Not stated

	(n=41) Intervention 2: Usual care. Received standard care offered to patients with co-existing diabetes and CKD attending the diabetes and nephrology outpatients' clinics at hospital. Blood pressure control was the most important aspect of standard care and care was dependent on the patients' individual circumstances and morbidity. Duration 12 mths (standard care). Concurrent medication/care: Not stated
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF MANAGEMENT SUPPORT SYSTEM versus USUAL CARE Protocol outcome 1: Progression of CKD (change in eGFR) (Important) at At stated in paper - Actual outcome: Final value eGFR at 3 mths; Other: 48 (95%CI 35 to 60.5) (Median (IQR)); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Final value eGFR at 12 mths; Other: 48 (95%CI 38 to 76) (Median (IQR)); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adherence to treatment at At stated in paper - Actual outcome: Adherence to medication at 12 months; Group 1: 24/36, Group 2: 25/39; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause and cardiovascular) (Critical) at At stated in paper; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at At stated in paper; Hospitalisation (Important) at At stated in paper; Outpatient attendance at At stated in paper; Health related quality of life (Important) at At stated in paper

G.9 Blood pressure - combined renin-angiotensin-aldosterone system antagonists

Table 83: Ahmad 1997

Study	Ahmad 1997[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in India; Setting: Outpatient endocrinology clinic
Line of therapy	1st line
Duration of study	Intervention time: 5 years on treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 43-55; diabetes <15 years; no non-diabetic renal, systemic, cardiac or hepatic disease; BMI <27kg/m^2; normal BP (less than or equal to 140.90mmHg); GFR >90ml/min; AER 20-200 microg/min or 2 consecutive visits without UTI
Exclusion criteria	None other
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 49.6 (5.2) years. Gender (M:F): 60 men + 43 women. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: Mixed 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) range eGFR: enalapril 124 (12.2) 95-148 ml/min/1.73m^2; placebo 124 (14.6) 92-149 ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: ACE inhibitors - Enalapril. Enalapril 10mg daily. Duration 5 years. Concurrent medication/care: 14 patients on diet alone; 29 oral antidiabetic agents; 9 insulin; normotensive, no other antihypertensive medication

Study	Ahmad 1997[22]
	(n=51) Intervention 2: Placebo. placebo . Duration 5 years. Concurrent medication/care: 12 diet alone, 31 oral antidiabetic agents, 8 insulin; normotensive, no other antihypertensive agents
Funding	Academic or government funding (Department of Science and Technology, Government of India)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: GFR at 5 years; Group 1: mean 119 ml/min/1.73m^2 (SD 12); n=46, Group 2: mean 119 ml/min/1.73m^2 (SD 15.5); n=44; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: AER (log transformed; geometric mean presented) at 5 years; Group 1: mean 20 microg/min (SD 59); n=46, Group 2: mean 85 microg/min (SD 90); n=44; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to clinical proteinuria (AER >200 microg/min) at 5 years; Group 1: 4/46, Group 2: 12/44; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 84: Ahmad 2003

Study	Ahmad 2003[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=73)

Study	Ahmad 2003[23]
Countries and setting	Conducted in India; Setting: Endocrinology outpatients
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AER 20-200 microg/min on two consecutive visits
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age <40 years; diabetes 5-15 years; no evidence of non-diabetic renal, systemic, cardiac or hepatic disease; stable BMI for last 3 months; stable HbA1c <9% last 3 months; BP <140/90mmHg on no antihypertensive treatment; GFR >90ml/min; AER 20-200 microg on 2 visits twoconsecutive
Exclusion criteria	Pulmonary TB, CVA, UTI, microscopic haematuria, clinila proteinuria
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Enalapril: 31.3 (3.2); placebo 31.7 (3.8). Gender (M:F): 38 men + 35 women. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) range eGFR: enalapril 131 (15.3) 95-147 ml/min/1.73m^2; placebo 130 (15.5) 97-155 ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: ACE inhibitors - Enalapril. Enalapril 10mg daily. Duration 5 years. Concurrent medication/care: Insulin mean dose 0.8 (0.2) IU/kg/24 hours; no antihypertensives (n=36) Intervention 2: Placebo. placebo. Duration 5 years. Concurrent medication/care: Insulin mean dose 0.8 (0.2) IU/kg/24 hours; no antihypertensives
Funding	Academic or government funding (Department of Science and Technology, India)

Study	Ahmad 2003[23]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: GFR at 5 years; Group 1: mean 126 ml/min/1.73m^2 (SD 15); n=37, Group 2: mean 121 ml/min/1.73m^2 (SD 20.1); n=36; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: AER (geometric mean) at 5 years; Group 1: mean 33 mg/24 hours (SD 31.5); n=37, Group 2: mean 215 mg/24 hours (SD 212.6); n=36; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to overt nephropathy at 5 years; Group 1: 3/37, Group 2: 11/36; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 85: Anand 2009

Study	Anand 2009[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Total 5010; CKD subgroup 2890)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean duration 23 months (range 0-38 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GFR < 60ml/min/1.73m^2
Stratum	Overall: Whole trial was patients with heart failure; CKD subgroup reported here

Study	Anand 2009[34]
Subgroup analysis within study	Post-hoc subgroup analysis: CKD patients
Inclusion criteria	Stable symptomatic heart failure, on HF therapy, LVEF <40%, LV internal diameter in diastole adjusted for body surface area 2.9cm/m^2 or more; GFR <60ml/min/1.73m^2
Exclusion criteria	Systolic BP <90mmHg; serum creatinine >2.5 mg/dL
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): CKD no proteinuria: 66 (9) years; CKD + proteinuria: 65 (10). Gender (M:F): 88% male. Ethnicity: 89% white
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) eGFR: CKD and proteinuria: 46 (10) ml/min/1.73m^2; CKD no proteinuria: 48 (9) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=1476) Intervention 1: Angiotensin-II receptor blockers - Valsartan. Valsartan initially 40mg twice daily, doubled every 2 weeks to reach target dose of 160mg twice daily provided systloic BP not below 90mmHg, no signs or symptoms of hypotension and serum creatinine did not exceed 150% of baseline value. Duration Mean 23 months (range 0-38 months). Concurrent medication/care: ACE inhibitors around 92%; beta blockers around 34%; diuretics around 90%; digoxin around 65%; spironolactone around 7% (not shown by intervention/control group) (n=1440) Intervention 2: Placebo. placebo. Duration mean 23 months (range 0-38 months). Concurrent medication/care: ACE inhibitors around 92%; beta blockers around 34%; diuretics around 90%; digoxin around 65%; spironolactone around 7% (not shown by intervention/control group)
Funding	Study funded by industry (Novartis Pharmaceuticals AG, Basel, Switzerland)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALSARTAN versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum	

Study	Anand 2009[34]
- Actual outcome: Mortality at Mean follow up 23 months; HR 1.01 (95%CI 0.85 to 1.2) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 86: Anon 1997

Study (subsidiary papers)	Anon 1997[2] (Ruggenenti 1999[594])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=352)
Countries and setting	Conducted in Italy; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Stratum 1: 31 months; Stratum 2: 16 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary protein excretion
Stratum	CKD without diabetes: Proteinuria 3g/24 hours or more; no diabetes
Subgroup analysis within study	Stratified then randomised: Proteinuria 3g/24 hours or more
Inclusion criteria	Normotensive (BP ,140/90mmHg without antihypertensive therapy) or hypertensive; 18-70 years; chronic nephropathy (creatinine clearance 20-70ml/min/1.73m^2; variation <30% in last 3 months) and persistent proteinuria (urinary protein excretion >1g/24 hours for at least 3 months without UTI or overt heart failure); no ACE inhibitors in last 2 months; serum potassium 3.5-5.0mmol/L; compliance >80% in run-in phase
Exclusion criteria	Steroids, NSAIDs or immunosuppressive drugs; acute MI or CVA in last 6 months; severe uncontrolled hypertension (diastolic BP 115mmHg or more and/or systolic BP 220mmHg or more); renovascular disease; obstructive uropathy; IDDM; collagen disease, cancer, raised serum aminotransferase; chronic cough; drug or alcohol abuse; pregnancy;

Study (subsidiary papers)	Anon 1997[2] (Ruggenenti 1999[594])
	breastfeeding; ineffective contraception
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Stratum 1: ramipril 49.1 (1.3); placebo 50.3 (1.5); Stratum 2: ramipril 48.9 (13.6); placebo 49.7 (13.6). Gender (M:F): 130/166 (78%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria : Mixed (Stratum 1: 1-2.9g/24 hours; stratum 2: 3g/24 hours or more).
Extra comments	Baseline measured GFR: ramipril 40.2 (19.0) ml/min/1.73m^2; placebo 37.4 (17.5) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=177) Intervention 1: ACE inhibitors - Ramipril. Ramipril 1.25mg, increased every 2 weeks until diastolic BP <90mmHg. Duration 16 months. Concurrent medication/care: In patients already on antihypertensives, study drug increased and other drug decreased to minimum dose. Antihypertensives (other than ACE inhibitors ACE inhibitors and ARBs) could be introduced and doses adjusted to achieve and maintain diastolic BP <90mmHg Comments: 99 Stratum 1; 78 Stratum 2 (n=175) Intervention 2: Placebo. Placebo. Duration 16 months. Concurrent medication/care: In patients already on antihypertensives, study drug increased and other drug decreased to minimum dose. Antihypertensives (other than ACEI and ARBs) could be introduced and doses adjusted to achieve and maintain diastolic BP <90mmHg Comments: 87 Stratum 1 + 88 Stratum 2
Funding	Study funded by industry (Hoechst Marion Roussel Clinical Research Institute, Frankfurt am Main, Germany)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD without diabetes: All-cause mortality (Stratum 2) at 16 months; Group 1: 2/78, Group 2: 1/88; Risk of bias: Low; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Anon 1997[2] (Ruggenenti 1999[594])
- Actual outcome for CKD without diabetes: Sudden death (Stratum 1) at 31 months; Group 1: 1/99, Group 2: 0/87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: Non-fatal cardiovascular events (Stratum 2) at 16 months; Group 1: 4/78, Group 2: 3/88; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Non-fatal CV events (Stratum 1) at 31 months; Group 1: 2/99, Group 2: 3/87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: Doubling serum creatinine or ESRD at 36 months; HR 0.54 (95%CI 0.32 to 0.92) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: ESRD (dialysis or transplant) Stratum 1 at 31 months; HR 0.35 (95%CI 0.16 to 0.78) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: GFR <45 ESRD (dialysis or transplant) Stratum 1 at 31 months; HR 0.39 (95%CI 0.16 to 0.94) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: Rate of GFR decline (stratum 2) at 16 months; Group 1: mean 0.53 ml/min/month (SD 0.6); n=56, Group 2: mean 0.88 ml/min/month (SD 1.01); n=61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Change in GFR per month (Stratum 1) at 31 months; Group 1: mean -0.26 ml/min/1.73m^2/month (SD 0.5); n=99, Group 2: mean -0.29 ml/min/1.73m^2/month (SD 0.6); n=87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Progression to macroalbuminuria (Stratum 1) at 31 months; Group 1: 15/99, Group 2: 27/87; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 87: Anon 2001

Study	Anon 2001[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in Italy, United Kingdom; Setting: Diabetic and renal centres
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AER 30-1500microg/min
Stratum	CKD with diabetes: Type 1 diabetes + AER 30-1500 microg/min
Subgroup analysis within study	Not applicable
Inclusion criteria	18-65 years; typ1 diabetes; AER 30-1500microg/min; GFR >70ml/min; serum creatinine <130 micromol/l; BP 150/90mmHg or less on no antihypertensive treatment; agreed to renal biopsy; compliance at least 85% during baseline period
Exclusion criteria	HbA1c >6SDs above local normal range; antihypertensive or NSAID therapy; hyperkalaemia, other renal or urinary tract disease, liver disease, recent CVA or cardiac disease; pregnancy, contraindication to renal biopsy
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 38 (20-64). Gender (M:F): 24 male + 12 female. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (range) eGFR: 103 (62-162) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: ACE inhibitors - Enalapril. Enalapril 10mg once daily. Duration 3 years. Concurrent medication/care: No other antihypertensives (n=18) Intervention 2: Placebo. placebo. Duration 3 years. Concurrent medication/care: No other antihypertensives

Study	Anon 2001[4]
Funding	Other (Northern Regional Health Authority, British Diabetic Association adn Merck, Sharp and Dohme, Herts UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: GFR rate of decline at 3 years; Other: 4.1 (95%CI 2.6 to 5.6) (Annual rate of decline of GFR); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 88: Arai 2008

Study	Arai 2008[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + hypertension + microalbuminuria
Subgroup analysis within study	Not applicable

Study	Arai 2008[38]
Inclusion criteria	Type 2 diabetes (on diet and exercise therapy), hypertension (BP 140/90mmHg or higher), early (stage 2) nephropathy defined as 30-299mg urinary albumin/24 hours
Exclusion criteria	None other
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Telmisartan 74.3 (4.4), valsartan 73.6 (5.0), candesartan 73.3 (5.5), losartan 72.6 (4.7). Gender (M:F): 40/80 (50%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline UAER candesartan: 82.3 (17.1) mg/d; losartan: 80.8 (19.2) mg/d; telmisartan 81.4 (18.3) mg/d; valsartan 80.0 (17.2) mg/d
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Angiotensin-II receptor blockers - Candesartan. Candesartan mean dose 10.2 (2.0) mg daily. Duration 12 months. Concurrent medication/care: 3/20 (15%) on statins (n=20) Intervention 2: Angiotensin-II receptor blockers - Losartan. Losartan mean dose 71.3 (21.9) mg daily. Duration 12 months. Concurrent medication/care: 2/20 (10%) on statins (n=20) Intervention 3: Angiotensin-II receptor blockers - Telmisartan. Telmisartan mean dose 48.0 (16.4) mg daily. Duration 12 months. Concurrent medication/care: 2/20 (10%) on statins (n=20) Intervention 4: Angiotensin-II receptor blockers - Valsartan. Valsartan mean dose 116.0 (40.8) mg daily. Duration 12 months. Concurrent medication/care: 1/20 (5%) on statins
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus LOSARTAN	

Study	Arai 2008[38]
Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 1: mean 81.2 mg/d (SD 33.4); n=20, Group 2: mean 74.2 mg/d (SD 31.5); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus TELMISARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 1: mean 81.2 mg/d (SD 33.4); n=20, Group 2: mean 57.2 mg/d (SD 27.1); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus VALSARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 1: mean 81.2 mg/d (SD 33.4); n=20, Group 2: mean 66 mg/d (SD 27.7); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus TELMISARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 1: mean 74.2 mg/d (SD 31.5); n=20, Group 2: mean 57.2 mg/d (SD 27.1); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus VALSARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 2: mean 66 mg/d (SD 27.7); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus VALSARTAN

Study	Arai 2008[38]
Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Group 1: mean 57.2 mg/d (SD 27.1); n=20, Group 2: mean 66 mg/d (SD 27.7); n=20; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 89: Bakris 2008

Study	Bakris 2008[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=860)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary protein: creatinine ratio
Stratum	CKD with diabetes: Type 2 diabetes and hypertension and macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 21-80 years; type 2 diabetes; HbA1c 10% or below; serum creatinine 3mg/dl or less for women or 3.2mg/dL or less for men; first morning spot urinary protein to creatinine (UPC) 700mg/g or more; BP 130/80mmHg or more or on antihypertensives
Exclusion criteria	Pregnant, nursing, surgically sterile and not using effective contraception; >35% increase in serum creatinine during

Study	Bakris 2008[52]
	washout or serum potassium >5meq; non-diabetic renal disease; clincially significant heart disease, stroke, renal artery stenosis, hepatic dysfunction, electrolyte imbalance; hypersensitivity to study drugs; on chronic immunosuppression
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Telmisartan 60 (9.2); losartan 60.5 (9.4) years. Gender (M:F): 62.2% male. Ethnicity: 47% Caucasian, 12% Black, 41% Asian
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) eGFR: telmisartan: 49.5 (21.6) ml/min/1.73m^2; losartan: 49.6 (22.4) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=419) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 40mg once daily for 2 weeks then 80mg daily. Duration 12 months. Concurrent medication/care: Additional antihypertensives excluding ARBs, ACEIs or direct vasodilators could be given following forced titration to achieve BP target of <130/80mmHg (n=441) Intervention 2: Angiotensin-II receptor blockers - Losartan. Losartan 50mg daily for first 2 weeks then 100mg daily. Duration 12 months. Concurrent medication/care: Additional antihypertensives excluding ARBs, ACEIs or direct vasodilators could be given following forced titration to achieve BP target of <130/80mmHg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus LOSARTAN

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: All-cause mortality at 12 months; Group 1: 2/419, Group 2: 13/441; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Cardiovascular morbidity or mortality at 12 months; Group 1: 21/419, Group 2: 37/441; Risk of bias: Low; Indirectness of

Study	Bakris 2008[52]
outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Doubling serum creatinine, ESRD or all-cause mortality at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Change in eGFR at 12 months; Group 1: mean -6.49 ml/min/1.73m^2 (SD 1.1); n=419, Group 2: mean -6.5 ml/min/1.73m^2 (SD 1.1); n=441; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin to creatinine ratio at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 90: Barnett 2004

Study	Barnett 2004[59]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes + HT + albuminuria

Study	Barnett 2004[59]
Subgroup analysis within study	Not applicable
Inclusion criteria	White or Asian; 35-80 years; type 2 diabetes treated by diet, diet + oral antidiabetic drugs (at least 1 year) or diet + insulin (at least 1 year; if on insulin, diabetes diagnosed after age 40 and BMI >25kg/m^2 at diagnosis); hypertension (BP <185/95mmHg after at least 3 months of ACEI; normal renal morphology; UAER 11-999microg/min; HbA1c<12%; serum creatinine <1.6mg/dL; GFR >70ml/min/1.73m^2
Exclusion criteria	Any condition other than cardiovascular disease that could restrict long-term survival and known allergy to study drugs or iohexol
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Telmisartan 61.2 (8.5); enalapril 60 (9.1). Gender (M:F): 182/250 (73%) male. Ethnicity: 98.4% white
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline measured mean (SD) GFR: telmisartan 91.4 (21.5) ml/min/1.73m^2; enalapril 94.3 (22.1) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=120) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 40mg once daily with forced titration after 4 weeks to 80mg once daily. Duration 5 years. Concurrent medication/care: 1 month screening period: patients received antihypertensive medication including ACEI; then this medication stopped and patients randomised; additional antihypertensive medication (not ACEI or ARB) allowed after 2 months if resting BP >160/100mmHg; initial target BP <160/90mmHg but lowered as guidelines changed during study; treatment of diabetes at investigator's discretion. During study: diuretics 52.5%, beta-blockers 39.2%, calcium channel blockers 45.8%, other antihypertensives 35%, aspirin 36.7%, statins 42.5% (n=130) Intervention 2: ACE inhibitors - Enalapril. Enalapril 10mg once daily with forced titration after 4 weeks to 20mg once daily. Duration 5 years. Concurrent medication/care: 1 month screening period: patients received antihypertensive medication including ACEI; then this medication stopped and patients randomised; additional antihypertensive medication (not ACEI or ARB) allowed after 2 months if resting BP >160/100mmHg; initial target BP <160/90mmHg but lowered as guidelines changed during study; treatment of diabetes at investigator's discretion. During study: diuretics 51.5%, beta-blockers 39.2%, calcium channel blockers 46.1%, other antihypertensives 35.4%,

Study	Barnett 2004[59]
	aspirin 41.5%, statins 41.5%
Funding	Study funded by industry (Boehringer Ingelheim)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus ENALAPRIL Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: All-cause mortality at 5 years; Group 1: 6/120, Group 2: 6/130; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Cardiovascular mortality at 5 years; Group 1: 3/120, Group 2: 2/130; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Stroke at 5 years; Group 1: 6/120, Group 2: 6/130; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Heart failure at 5 years; Group 1: 9/120, Group 2: 7/130; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Myocardial infarction at 5 years; Group 1: 9/120, Group 2: 6/130; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Mean change in GFR at 5 years; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion: ratio of final to baseline value at 5 years; Other: 1.04 (95%CI 0.71 to 1.51) (Ratio of difference between groups); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 91: Bilic 2011

Study	Bilic 2011[78]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=71)
Countries and setting	Conducted in Croatia; Setting: Outpatient renal department
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Established by patient history, physical examination, urinalysis, serum biochemistry tests and renal biopsy
Stratum	CKD without diabetes: CKD; diabetes excluded
Subgroup analysis within study	Not applicable
Inclusion criteria	18 to 60 years of age, nondiabetic nephropathy, and persistent proteinuria (>=0.5 g/day) for a minimum of 3 months after first visit, without evidence of urinary tract infection or heart failure.
Exclusion criteria	Treatment with nonsteroidal anti-inflammatory drugs, renal failure, acute myocardial infarction or stroke, severe uncontrolled hypertension, chronic pulmonary disease, evidence or suspician or renovascular disease, obstructive uropathy, diabetes mellitus, cancer, pregnancy, and infectious disease.
Recruitment/selection of patients	Consective renal patients were screened for inclusion between Feb 2001 and May 2003.
Age, gender and ethnicity	Age - Mean (SD): ACEI: 46.3 (16.4); ARB: 47.4 (16.9); ACE + ARB: 46.1 (18.3). Gender (M:F): Not reported. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	. 4 week wash-out period in patients taking ACE inhibitors or ARB and 2 weeks in patients without antihypertensive treatment. Baseline GFR not stated; baseline mean (SD) proteinuria: ramipril: 4.9 (6.5) g/d; valsartan: 3.7 (3.9) g/d; ramipril + valsartan: 5.5 (6.1) g/d
Indirectness of population	No indirectness

Study	Bilic 2011[78]
Interventions	(n=26) Intervention 1: ACE inhibitors and Angiotensin-II receptor blockers - Ramipril and Valsartan. 5 mg/day ramipril plus 80 mg/day valsartan. Duration 12 months. Concurrent medication/care: Urapidil (no details on dose reported); none of the patients were on calcium channel blockers (n=23) Intervention 2: ACE inhibitors - Ramipril. 5 mg/day (increased to 10mg/day in a few patients). Duration 12 months. Concurrent medication/care: Urapidil (no details provided on dose) (n=22) Intervention 3: Angiotensin-II receptor blockers - Valsartan. 80 mg/day (increased to 180 mg/day in a few patients). Duration 12 months. Concurrent medication/care: Urapidil (no detail on dose reported)
Funding	Academic or government funding (Supported by funds from the Scientific project of Ministry of science, education and sports Republic of Croatia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL AND VALSARTAN versus RAMIPRIL

Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum
- Actual outcome for CKD without diabetes: Creatinine clearance (ml/min) at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD without diabetes: Proteinuria in 24-h urine sample at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL AND VALSARTAN versus VALSARTAN

Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum
- Actual outcome for CKD without diabetes: Creatinine clearance (ml/min) at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD without diabetes: Proteinuria in 24-h urine sample at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study	Bilic 2011[78]
- Actual outcome for CKD without diabetes: 12 hour sample at 6 months; Risk of bias: ; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus VALSARTAN Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: Creatinine clearance (ml/min) at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Proteinuria in 24-h urine sample at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 92: Bojestig 2001

Study	Bojestig 2001[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=55)
Countries and setting	Conducted in Sweden; Setting: Outpatient centres
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion rate
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable

Study	Bojestig 2001[86]
Inclusion criteria	Type 1 diabetes; normotensive (diastolic BP <90mmHg); microalbuminuria (UAER 20-200 microg/min in two of three urine collections)
Exclusion criteria	On antihypertensive drugs
Recruitment/selection of patients	Consecutively recruited
Age, gender and ethnicity	Age - Mean (SD): Ramipril 5mg: 39 (10), ramipril 1.25mg: 42 (10), placebo: 38 (9) . Gender (M:F): 41/55 (75%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline median (range) eGFR: ramipril 1.25mg: 100 (63-144) ml/min/1.73m^2; ramipril 5mg: 100 (69-134) ml/min/1.73m^2; placebo 108 (49-138) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: ACE inhibitors - Ramipril. Ramipril 5mg once daily in the morning. Duration 2 years. Concurrent medication/care: No antihypertensives; other medication not stated (n=19) Intervention 2: ACE inhibitors - Ramipril. Ramipril 1.25mg once daily in the morning. Duration 2 years. Concurrent medication/care: No antihypertensives; other medication not stated (n=18) Intervention 3: Placebo. Placebo. Duration 2 years. Concurrent medication/care: No antihypertensives; other medication not stated
Funding	Study funded by industry (Hoechst AG, later Aventis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO

Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: GFR (ramipril 5mg) at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: GFR (ramipril 1.25mg) at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Bojestig 2001[86]
Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: UAER (ramipril 5mg) at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: UAER (ramipril 1.25mg) at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 93: Brenner 2001

Study	Brenner 2001[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1513)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean 3.4 years (range 2.3 to 4.6)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin:creatinine ratio, urinary protein
Stratum	CKD with diabetes: Type 2 diabetes and macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 31-70 years; type 2 diabetes; nephropathy (on 2 occasions urinary albumin [mg/L] to creatinine [g/L] of at least 300 or urinary protein excretion rate of 0.5g/day and serum creatinine 1.3 to 3.0mg/dL [or lower limit 1.5 for males >60kg])
Exclusion criteria	Type 1 diabetes or non-diabetic renal disease including renal artery stenosis; MI or CABG in previous month; CVA or PTCA in previous 6 months; TIA in previous year; history of heart failure

Study	Brenner 2001[93]
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Losartan 60 (7); placebo 60 (7). Gender (M:F): 63.2% male. Ethnicity: Asian 16.7%; Black 15.2%; White 48.6%; Hispanic 18.2%; Other 1.3%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline median urinary albumin:creatinine ratio: losartan 1237; placebo 1261
Indirectness of population	No indirectness
Interventions	(n=751) Intervention 1: Angiotensin-II receptor blockers - Losartan. Losartan initial dose 50mg once daily, increased to 100mg after 4 weeks if BP >140/90mmHg (71% received 100mg). Duration 3.4 years. Concurrent medication/care: During 6 week screening phase, patients continued antihypertensive drugs except ACEI and ARB replaced with diuretics, calcium channel antagonists, alpha- or beta-blockers, centrally acting agents or combination of these. Randomisation and dose titration of losartan at 4 weeks. After additional 8 weeks, further antihypertensives from these classes could be added if BP > 140/90mmHg. During study: diuretics 83.8%, calcium channel antagonists 77.9%, alpha-blockers 40.2%, beta-blockers 34.1%, centrally acting agents 18.0% (n=762) Intervention 2: Placebo. Placebo. Duration 3.4 years. Concurrent medication/care: During 6 week screening phase, patients continued antihypertensive drugs except ACEI and ARB replaced with diuretics, calcium channel antagonists, alpha- or beta-blockers, centrally acting agents or combination of these. Randomisation and dose titration at 4 weeks. After additional 8 weeks, further antihypertensives from these classes could be added if BP > 140/90mmHg. During study: diuretics 84.0%, calcium channel antagonists 81.1%, alpha-blockers 45.7%, beta-blockers 36.7%, centrally acting agents 21.7%
Funding	Study funded by industry (Merck and Company)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum	

Study	Brenner 2001[93]
- Actual outcome for CKD with diabetes: Mortality at 3.4 years; Group 1: 158/748, Group 2: 155/762; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Fatal or non-fatal cardiovascular event (MI, stroke, first hospitalisation for heart failure or unstable angina, coronary or peripheral revascularisation or cardiovascular mortality) at 3.4 years; Group 1: 247/748, Group 2: 268/762; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Myocardial infarction at 3.4 years; Group 1: 50/748, Group 2: 68/762; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (dialysis or transplant) at 3.4 years; HR 0.71 (95%CI 0.57 to 0.89) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Doubling of serum creatining at 3.4 years; HR 0.77 (95%CI 0.62 to 0.95) Calculated – from Kaplan Meier curve; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 5: Hospitalisation (Important) at 12 months minimum - Actual outcome for CKD with diabetes: First hospitalisation for heart failure at 3.4 years; HR 0.67 (95%CI 0.51 to 0.88) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 94: Crepaldi 1998

Study	Crepaldi 1998[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)

Study	Crepaldi 1998[144]
Countries and setting	Conducted in Italy; Setting: Outpatient centres
Line of therapy	Unclear
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	18-65 years; type 1 diabetes diagnosed <35 years; insulin within 3 years of diagnosis; HbA1c<11% and within 30% of entry value for past 12 months; standing systolic BP 115-140mmHg without anithypertensive drugs and diastolic 75-90mmHg; median AER 20-200 microg/min 3 times in previous year and 3 times within 2 weeks of entry; GFR 80ml/min/1.73m^2
Exclusion criteria	Impaired renal function (serum creatinine >10% above ULN and median AER >200microg/min); history of non-diabetic renal disease; haematuria; clinically significant liver or haematological disease; aortic or mitral valve obstruction; arrhythmia; unstable angina; MI in last 3 months; autonomic neuropathy; malignancy; hyperkalaemia (>5.5mmol/L); triglycerides >3.4mmol/L; total cholesterol >6.5mmol/L; familial lipid disorder; risk of transmitting AIDS/viral hepatitis; hypersensitivity/contraindications to study drugs; childbearing potential (oral contraceptives not allowed) or planning pregnancy; compliance <85% in run in period; antihypertensive drugs
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Lisinopril 38 (11); placebo 37 (10). Gender (M:F): 44/66 (67%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) measured GFR: lisinopril 122 (14) ml/min/1.73m^2; placebo 107 (20) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: ACE inhibitors - Lisinopril. Lisinopril 10mg once daily; doubled if systolic and diastolic BP not reduced by 5% of baseline values after 1 month. Duration 3 years. Concurrent medication/care: No baseline antihypertensives; if 3 months after randomisation systolic and diastolic BP not reduced by 5% of baseline values and standing BP >140/90mmHg on 2 consecutive visits on higher dose of study drug, atenolol 50mg once daily added. If BP

Study	Crepaldi 1998[144]
	>140/90mmHg at any subsequent visit, atenolol doubled to 100mg once daily. If BP >160/90mmHg, patient withdrawn. Continued usual insulin. (n=34) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: No baseline antihypertensives; if 3 months after randomisation systolic and diastolic BP not reduced by 5% of baseline values and standing BP >140/90mmHg on 2 consecutive visits on higher dose of study drug, atenolol 50mg once daily added. If BP >140/90mmHg at any subsequent visit, atenolol doubled to 100mg once daily. If BP >160/90mmHg, patient withdrawn. Continued usual insulin.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression to clinical albuminuria (AER >200microg/min) at 3 years; Group 1: 2/32, Group 2: 7/34; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: AER at 3 years; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (AER <20microg/min) at 3 years; Group 1: 4/30, Group 2: 1/28; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 95: Fernandez 2013

Study	Fernandez 2013[199]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=133)
Countries and setting	Conducted in Spain; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urine protein-creatinine ratio
Stratum	CKD with diabetes: Type 2 diabetes + macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	>35 years; type 2 diabetes; diabetic nephropathy, stage 2 or 3 chronic kidney disease, urine protein-creatinine ratio >300mg/g on morning spot sample on 2 occasions; serum potassium <5.5mEq/L; HbA1c <10%; proteinuria with protein excretion <10g/24 hours; blood albumin >2g/dL; hypertension BP <180/95mmHg
Exclusion criteria	MI, stroke, heart failure, or myocardial revascularisation in last 3 months; any condition that could restrict long-term survival
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Lisinopril 68.7 (6.8); irbesartan 67.9 (8.0); lisinopril + irbesartan 63.0 (8.5): combination group significantly younger p<0.05. Gender (M:F): 75% male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) eGFR: lisinopril 48 (14) ml/min/1.73m^2; irbesartan 46 (16) ml/min/1.73m^2; lisinopril + irbesartan 50 (25) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: ACE inhibitors - Lisinopril. Lisinopril 10mg once daily, titrated up to maximum 40mg after 8 weeks; 92% reached final recommended dose. Duration 32 months. Concurrent medication/care: 4-week washout

Study	Fernandez 2013[199]
	period: patients continued usual antihypertensive except ACEI or ARB replaced by alternative drugs. Received "standard of care" for diabetes. (n=28) Intervention 2: Angiotensin-II receptor blockers - Irbesartan. Irbesartan 150mg, titrated up to maximum 600mg after 8 weeks; 93% reached final recommended dose. Duration 32 months. Concurrent medication/care: 4-week washout period: patients continued usual antihypertensive except ACEI or ARB replaced by alternative drugs. Received "standard of care" for diabetes. (n=70) Intervention 3: ACE inhibitors and Angiotensin-II receptor blockers - Lisinopril and Irbesartan. Lisinopril 5mg + irbesartan 75mg, titrated up to maximum lisinopril 20mg + irbesartan 300mg after 8 weeks; 96% reached final recommended dose. Duration 32 months. Concurrent medication/care: 4-week washout period: patients continued usual antihypertensive except ACEI or ARB replaced by alternative drugs. Received "standard of care" for diabetes.
Funding	Other (Spanish Ministry of Science and Innovation, Spanish Society of Nephrology, Bristol Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL versus IRBESARTAN

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Mortality at 32 months; Group 1: 2/35, Group 2: 1/28; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: ESRD (dialysis or transplant) at 32 months; Group 1: 6/35, Group 2: 5/28; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Rate of decrease in GFR at 32 months; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Urine protein-creatinine ratio (geometric mean) at 12 months; Group 1: mean 0.68 g/g (SD 0.42); n=35, Group 2: mean 1.01

Study	Fernandez 2013[199]
g/g (SD 0.57); n=28; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL AND IRBESARTAN versus LISINOPRIL Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Mortality at 32 months; Group 1: 6/70, Group 2: 2/35; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (dialysis or transplant) at 32 months; Group 1: 10/70, Group 2: 6/35; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Rate of decrease in GFR at 32 months; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urine protein-creatinine ratio (geometric mean) at 12 months; Group 1: mean 1.04 g/g (SD 0.33); n=70, Group 2: mean 0.68 g/g (SD 0.42); n=35; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL AND IRBESARTAN versus IRBESARTAN Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Mortality at 32 months; Group 1: 6/70, Group 2: 1/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (dialysis or transplant) at 32 months; Group 1: 10/70, Group 2: 5/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Rate of decrease in GFR at 32 months; Risk of bias: High; Indirectness of outcome: No indirectness	

Study	Fernandez 2013[199]
Protocol outcome 4: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urine protein-creatinine ratio (geometric mean) at 12 months; Group 1: mean 1.04 g/g (SD 0.33); n=70, Group 2: mean 1.01 g/g (SD 0.57); n=28; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 96: Galle 2008

Study	Galle 2008[217]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=885)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Proteinuria 900mg/24 hours or more
Stratum	CKD with diabetes: Type 2 diabetes + HT + macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	30-80 years; type 2 diabetes; HbA1c 10% or less; overt nephropathy (serum creatinine 3.0mg/dL or less and proteinuria 900mg/24 hours or more); hypertension (BP > 130/80mmHg or on antihypertensives
Exclusion criteria	Premenopausal women not surgically sterile/using acceptable contraception/pregnant/breastfeeding; recent acute CV event; congestive heart failure; reciept of metformin if elevated serum creatinine; non-diabetic renal disease; >30% increase in serum creatinine in run-in period; secondary hypertension; hepatic dysfunction; biliary obstructive disorders; renal artery stenosis; chronic immunosuppressive therapy; drug or alcohol dependency; systolic BP > 180mmHg and/or distolic BP >110mmHg on 2 consecutive visits during run-in

Study	Galle 2008[217]
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Telmisartan 60.9 (9.2); valsartan 61.4 (9.1). Gender (M:F): 64.1% male. Ethnicity: Asian 19.1%; Black 1.8%; White 79.1%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline geometric mean (SD) eGFR: telmisartan 56.7 (26.3) ml/min/1.72 m^2; valsartan 56.5 (25.4) ml/min/1.72 m^2
Indirectness of population	No indirectness
Interventions	(n=443) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 40mg once daily, increased after 2 weeks in all patients to 80mg once daily. Duration 12 months. Concurrent medication/care: 2 weeks screening and 2 weeks placebo run-in to wash out ACEI and ARB; alternatives allowed other than direct vasodilators; after titration, additional antihypertensives allowed other than ACEI or ARB if BP <130/80mmHg. Statins 45.1%, other lipid-lowering drugs 8.4%, oral antidiabetic drugs 58.2%, insulin 58.7%, diuretic 92.1%, diuretic + beta-blocker 3.8%, beta-blocker 48.8%, calcium channel blocker 93.2%, calcium channel blocker + beta-blocker 0.7%, other antihypertensives 54.6% (n=442) Intervention 2: Angiotensin-II receptor blockers - Valsartan. Valsartan 80mg once daily, increased to 160mg after 2 weeks in all patients.. Duration 12 months. Concurrent medication/care: 2 weeks screening and 2 weeks placebo run-in to wash out ACEI and ARB; alternatives allowed other than direct vasodilators; after titration, additional antihypertensives allowed other than ACEI or ARB if BP <130/80mmHg. Statins 44.6%, other lipid-lowering drugs 10.9%, oral antidiabetic drugs 57%, insulin 56.8%, diuretic 94.1%, diuretic + beta-blocker 9%, beta-blocker 51.4%, calcium channel blocker 94.8%, calcium channel blocker + beta-blocker 1.8%, other antihypertensives 58.6%
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus VALSARTAN

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: All-cause mortality at 12 months; Group 1: 15/428, Group 2: 8/429; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Galle 2008[217]
- Actual outcome for CKD with diabetes: Cardiovascular mortality at 12 months; Group 1: 8/428, Group 2: 6/429; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Myocardial infarction at 12 months; Group 1: 4/428, Group 2: 11/429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Stroke at 12 months; Group 1: 11/428, Group 2: 5/429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: First hospitalisation for heart failure at 12 months; Group 1: 7/428, Group 2: 6/429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: First hospitalisation for unstable angina at 12 months; Group 1: 4/428, Group 2: 5/429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: First hospitalisation for coronary revascularisation at 12 months; Group 1: 3/428, Group 2: 5/429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: First hospitalisation for peripheral revascularisation at 12 months; Group 1: 2/428, Group 2: 2/429; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (dialysis, transplant or serum creatinine 6mg/dL or more) at 12 months; Group 1: 7/428, Group 2: 8/429; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: eGFR at 12 months; Group 1: mean 45.8 ml/min/1.73m^2 (SD 22.7); n=428, Group 2: mean 46.5 ml/min/1.73m^2 (SD 22.3); n=429; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary protein excretion rate at 12 months; Group 1: mean -33 % (SD 6.1); n=428, Group 2: mean -33 % (SD 5.6); n=429; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 12 months; Group 1: mean -39 % (SD 6.1); n=428, Group 2: mean -36 % (SD 6.1); n=429; Risk of bias: Low; Indirectness of outcome: No indirectness	

Study	Galle 2008[217]
Protocol outcomes not reported by the study	Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 97: Imai 2011

Study	Imai 2011[294]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=566)
Countries and setting	Conducted in Hong Kong (China), Japan; Setting: Outpatient clinics
Line of therapy	Mixed line
Duration of study	Intervention time: Mean 3.2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin:creatinine ratio
Stratum	CKD with diabetes: Type 2 diabetes; UACR >300mg/g
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 2 diabetes; age 30-70 years; urinary albumin:creatinine ratio >33.9mg/mmol (>300mg/g) in first morning sample; serum creatinine 1.0-2.5mg/dL in women or 1.2-2.5mg/dL in men
Exclusion criteria	Type 1 diabetes; MI or CABG in last 3 months; PCI, carotid or peripheral artery revascularisation within 6 months; stroke or TIA within 1 year; unstable angina or heart failure NYHA class III or IV; rapidly progressive renal disease within 3 months; severe orthostatic hypotension; serum potassium 3.5mmol/L or less or 5.5mmol/L or more
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Olmesartan 59.1 (8.1); placebo 59.2 (8.1). Gender (M:F): 391/566 (69.1%) male. Ethnicity: Japanese 65%; Chinese 35%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :

Study	Imai 2011[294]
Extra comments	Baseline GFR not reported; baseline median (IQR) urinary albumin:creatinine ratio: olmesartan 192.3 (87.1-339.4) mg/mmol; placebo 191.2 (98.4-352.9) mg/mmol
Indirectness of population	No indirectness
Interventions	(n=282) Intervention 1: Angiotensin-II receptor blockers - Olmesartan. Olmesartan 10mg once daily, titrated to 20mg once daily if BP not <130/85mmHg at 4 weeks, and further titrated to 40mg once daily. Every reasonable attempt made to up-titrate test drug to maximum dose even if target BP reached. 63.4% on 40mg at week 144. Duration 3.2 years. Concurrent medication/care: Patients already on ACEI at baseline (72.7%) could continue the same dose but ACEI could not be added after enrolment. Additional antihypertensives (diuretics 38.3%, beta-blockers 19.1%, calcium channel blockers 66.0%, alpha blockers 14.5% and others 13.1%) could be used but not potassium-sparing diuretics or ARBs. (n=284) Intervention 2: Placebo. Placebo. Duration 3.2 years. Concurrent medication/care: Patients already on ACEI at baseline (73.6%) could continue the same dose but ACEI could not be added after enrolment. Additional antihypertensives (diuretics 34.9%, beta-blockers 14.8%, calcium channel blockers 69.7%, alpha blockers 14.4% and others 13.4%) could be used but not potassium-sparing diuretics or ARBs.
Funding	Study funded by industry (Daiichi Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OLMESARTAN versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: All-cause mortality at 3.2 years; HR 0.99 (95%CI 0.53 to 1.86) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Cardiovascular mortailty at 3.2 years; HR 2.81 (95%CI 0.76 to 10.38) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Non-fatal stroke at 3.2 years; HR 0.73 (95%CI 0.29 to 1.83) Reported; Risk of bias: Low; Indirectness of outcome: No

Study	Imai 2011[294]
indirectness - Actual outcome for CKD with diabetes: Non-fatal MI at 3.2 years; HR 0.45 (95%CI 0.11 to 1.75) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Coronary, carotid or peripheral revascularisation at 3.2 years; HR 0.35 (95%CI 0.15 to 0.8) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Amputation at 3.2 years; Group 1: 4/282, Group 2: 0/284; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (SCr >5mg/dL, dialysis, transplantation) at 3.2 years; HR 1.08 (95%CI 0.78 to 1.49) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Hospitalisation (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Hospitalisation for unstable angina at 3.2 years; HR 1.37 (95%CI 0.31 to 6) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Hospitalisation for heart failure at 3.2 years; HR 0.59 (95%CI 0.32 to 1.1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Acute kidney injury (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Discontinuation due to acute renal failure at 3.2 years; Group 1: 1/282, Group 2: 1/284; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 98: Jerums 2004

Study	Jerums 2004[317]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)

Study	Jerums 2004[317]
Countries and setting	Conducted in Australia; Setting: Outpatient clinics
Line of therapy	Unclear
Duration of study	Intervention time: Median 66 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 15-65 years; type 2 diabetes for at least 1 year; microalbuminuria (2/3 consecutive measurements of AER 20-200microg/min on overnight samples); supine BP <140/90mmHg
Exclusion criteria	Non-diabetic renal disease; serum creatinine 200microM or more; haematuria; cardiac failure; hypertension; systemic disease; HbA1c >10%, serum potassium >5mM; recurrent UTI; at risk of pregnancy; other condition which might pose a risk to the patient or confound the results
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Perindopril 50 (2); placebo 53 (1). Gender (M:F): 29/50 (58%) male. Ethnicity: Caucasian 90%; Asian 10%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline measured mean (SEM) GFR: perindopril: 92 (8); placebo 98 (6) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: ACE inhibitors - Perindopril. Perindopril 2mg once daily in the morning then titrated at 2-weekly intervals to 4mg, then 8mg, aiming for a reduction in supine diastolic BP 5mmHg or more. Final dose achieved not stated. Duration 6 years. Concurrent medication/care: Lipid treatment 59%; other antihypertensive drugs: 1/18 at 24 months; 0/15 at 48 months and 2/11 at 72 months (n=27) Intervention 2: Placebo. Placebo. Duration 6 years. Concurrent medication/care: Lipid treatment 64%; other antihypertensive drugs: 2/22 at 24 months; 10/20 at 48 months and 10/15 at 72 months

Study	Jerums 2004[317]
Funding	Other (Servier IRIS, Paris, France and Diabetes Australia Research Trust)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Reversal microalbuminuria to normoalbuminuria at 72 months; Group 1: 1/11, Group 2: 3/15; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Microalbuminuria to macroalbuminuria at 72 months; Group 1: 2/11, Group 2: 7/15; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 99: Kanno 2006

Study	Kanno 2006[327]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean 3.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Daily urine protein excretion

Study	Kanno 2006[327]
Stratum	CKD without diabetes: Hypertension + proteinuria (diabetes excluded)
Subgroup analysis within study	Not applicable
Inclusion criteria	Hypertension (systolic BP > 130 and <180mmHg; diastolic >80 and <120mmhg); serum creatinine 1.2-5.0mg/dL; daily urine protein excretion >1.0g; on ACEI
Exclusion criteria	None other
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Candesartan + ACEI 60.3 (11.9); ACEI 59.9 (12.0). Gender (M:F): 36/90 (40%) male. Ethnicity: Japanese
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline mean (SEM) urinary protein excretion: candesartan + ACEI: 1.78 (0.10) g/d; ACEI: 1.61 (0.11) g/d
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: ACE inhibitors and Angiotensin-II receptor blockers - ACEI (mixed) and Candersartan. Candesartan 2-12mg daily; mean final dose 8.5 (1.2)mg/day. ACEI: benazepril (mean dose 4.5 [1.1]mg) or trandolapril (mean dose 2.4 [0.9]mg). Duration 3.1 years. Concurrent medication/care: Diuretics 15.5%; beta-blockers 6.7%; calcium antagonists 66.7%; others 17.8% (n=45) Intervention 2: ACE inhibitors - Trandolapril. ACEI: benazepril (mean dose 4.2 [0.9]mg) or trandolapril (mean dose 2.8 [1.2]mg). Duration 3.1 years. Concurrent medication/care: Diuretics 17.8%; beta-blockers 4.4%; calcium antagonists 62.2%; others 6.7%
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACEI (MIXED) AND CANDERSARTAN versus TRANDOLAPRIL	

Study	Kanno 2006[327]
Protocol outcome 1: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: Dialysis at 3 years; Group 1: 2/45, Group 2: 2/45; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Urinary protein excretion at 3 years; Group 1: mean 0.55 g/d (SD 0.16); n=45, Group 2: mean 1.21 g/d (SD 0.17); n=45; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 100: Katayama 2002

Study	Katayama 2002[332]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 1.48 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 1 diabetes diagnosed before age 20; age 20-50 years; UAE >30mg/day in 2 consecutive overnight urine samples; in hypertensive cases, diastolic BP <90mmHg with antihypertensives other than ACEI, calcium channel blockers or ARBs

Study	Katayama 2002[332]
Exclusion criteria	HbA1c>10%; serum creatinine >2mg/dL and other renal, endocrine, cardiac, liver, gastrointestinal or connective tissue diseases
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Captopril 30.9 (8.5); imidapril 36.2 (6.7); placebo 33.4 (7.9). Gender (M:F): 28/79 (35%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not reported; baseline mean (SD) albumin excretion: captopril: 550 (736) mg/d; imidapril 969 (1746) mg/d; placebo 619 (750) mg/d
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: ACE inhibitors - Captopril. Captopril 27.5mg. Duration 1.48 years. Concurrent medication/care: Not stated. Target systolic BP <140mmHg of baseline <150mmHg; <150mmHg if baseline 150-170mmHg; <160mmHg if baseline >170mmHg; hypotensive drugs other than ACEI, calcium channel blockers or ARBs added or dosage increased. (n=26) Intervention 2: ACE inhibitors - Imidapril. Imidapril 5mg daily. Duration 1.48 years. Concurrent medication/care: Not stated. Target systolic BP <140mmHg of baseline <150mmHg; <150mmHg if baseline 150-170mmHg; <160mmHg if baseline >170mmHg; hypotensive drugs other than ACEI, calcium channel blockers or ARBs added or dosage increased. (n=27) Intervention 3: Placebo. Placebo. Duration 1.48 years. Concurrent medication/care: Not stated. Target systolic BP <140mmHg of baseline <150mmHg; <150mmHg if baseline 150-170mmHg; <160mmHg if baseline >170mmHg; hypotensive drugs other than ACEI, calcium channel blockers or ARBs added or dosage increased.
Funding	Academic or government funding (Ministry of Health and Welfare and Research on Health Sciences focusing on Drug Innovation, Japan Health Sciences Foundation)

Study	Katayama 2002[332]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome: Percentage change in UAE at 1.48 years; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IMIDAPRIL versus CAPTOPRIL Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome: Percentage change in UAE at 1.48 years; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IMIDAPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome: Percentage change in UAE at 1.48 years; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 101: Lacourciere 2000

Study	Lacourciere 2000[364]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in Canada; Setting: Outpatients
Line of therapy	Mixed line

Study	Lacourciere 2000[364]
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + micro- or macro-albuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 2 diabetes diagnosed age 30 or later; hypertension (sitting diastolic BP 90-115mmHg); UAE 20-350microg/min without evidence of UTI
Exclusion criteria	Renovascular disease; malignant hypertension; systolic BP > 210mmHg; CVA or MI in last 12 months; current TIAs; clinically significant AV conduction disturbances and/or arrhythmias; unstable angina; history of heart failure; serum creatinine 200mmol/L or more; serum potassium 5.5mmol/L or more, or 3.5mol/L or less; steroids; drugs affecting BP except beta-blockers and nitrates for stable angina; drug or alcohol abuse; pregnancy, breastfeeding, ineffective contraception
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Losartan 59.2 (9.2); enalapril 57.8 (10.5). Gender (M:F): 83/103 (81%) male. Ethnicity: Caucasian 96%; Oriental 3%; Black 1%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR (geometric mean): losartan 96.7 ml/min; enalapril 95.3 ml/min
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Angiotensin-II receptor blockers - Losartan. Losartan 50mg; at week 8, doubled to 100mg if sitting diastolic BP >85mmHg. Mean dose 86.3 (22.5) mg at 12 months.. Duration 12 months. Concurrent medication/care: At week 12, if sitting diastolic BP >85mmHg, hydrochlorothiazide added (12.5mg titrated to 25mg); other antihypertensive drugs could also be added (other than ACEI or ARB or calcium channel blockers). At week 52, 31/52 (59.6%) on hydrochlorothiazide (mean dose 23.0 [4.7] mg), including 12/52 (23%) on triple therapy (hydrochlorothiazide plus beta- or alpha1-adrenoceptor blockers). Usual insulin or oral antidiabetic drugs. (n=51) Intervention 2: ACE inhibitors - Enalapril. Enalapril 5mg once daily; at 4 weeks, titrated up to 10mg once daily if

Study	Lacourciere 2000[364]
	sitting diastolic BP >85mmHg; at 8 weeks, titrated up to 20mg once daily if sitting diastolic BP >85mmHg. Mean dose at 12 months: 16.0 (6.2) mg. Duration 12 months. Concurrent medication/care: At week 12, if sitting diastolic BP >85mmHg, hydrochlorothiazide added (12.5mg titrated to 25mg); other antihypertensive drugs could also be added (other than ACEI or ARB or calcium channel blockers). At week 52, 26/51 (51%) on hydrochlorothiazide (mean dose 21.6 [5.7] mg), including 5/51 (5.8%) on triple therapy (hydrochlorothiazide plus beta- or alpha1-adrenoceptor blockers). Usual insulin or oral antidiabetic drugs.
Funding	Study funded by industry (Merck Frosst Canada & Co)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus ENALAPRIL Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: GFR at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Albuminuria at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 102: Laffel 1995

Study	Laffel 1995[365]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=143)

Study	Laffel 1995[365]
Countries and setting	Conducted in Canada, USA; Setting: Outpatient clinics
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Overnight urinary albumin excretion rate
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 14 to 57 years; 4 to 33 years of type 1 diabetes diagnosed before age 45 (history of ketonuria and continuous need for insulin except for periods <6 months in first 2 years after diagnosis); overnight UAE 20-200microg/min
Exclusion criteria	HbA1c 11.5% or more; body weight outside 75-125% ideal; serum creatinine and potassium levels outside normal ranges; WBC <3500/mm3; BP 140/90mmHg or more; antihypertensive therapy; pregnancy, lactation or inadequate contraception for women of childbearing age; history of renal, cardiac, hepatic, gastrointestinal or autoimmune disease; use of calcium cahnnel blockers, beta-blockers or NSAIDs (except low dose aspirin <650mg/day)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 32.7 (14 to 57). Gender (M:F): 72/143 (50.3%) male. Ethnicity: 91.6% white
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not reported; baseline geometric mean (SD) AER: captopril: 62 (36) microg/min; placebo 62 (41) microg/min
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: ACE inhibitors - Captopril. Captopril 50mg twice daily. Duration 24 months. Concurrent medication/care: Usual diet and insulin treatment. If BP 140/90mmHg or more at two consecutive vists, prazosin or clonidine added. (n=73) Intervention 2: Placebo. Placebo. Duration 24 months. Concurrent medication/care: Usual diet and insulin treatment. If BP 140/90mmHg or more at two consecutive vists, prazosin or clonidine added.

Study	Laffel 1995[365]
Funding	Study funded by industry (Bristol-Myers Squibb)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression microalbuminuria to clinical proteinuria at 24 months; HR 0.3 (95%CI 0.1 to 0.93) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Albumin excretion rate at 24 months; Group 1: mean -42.4 % (SD 90); n=67, Group 2: mean 13.5 % (SD 166); n=70; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 103: Lebovitz 1994-1

Study (subsidiary papers)	Lebovitz 1994-1[371] (Lebovitz 1994-2[371])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Total study: 121; macroalbuminuria subgroup 46; microalbuminuria subgroup 38)
Countries and setting	Conducted in USA; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion, serum creatinine, creatinine clearance

Study (subsidiary papers)	Lebovitz 1994-1[371] (Lebovitz 1994-2[371])
Stratum	CKD with diabetes: Type 2 diabetes + micro- or macro-albuminuria
Subgroup analysis within study	Post-hoc subgroup analysis: Group I: UAE <30mg/24 hours (<20microg/min); Group II: UAE 30-300mg/24 hours (20-200 microg/min); Group III: UAE >300mg/24 hours (>200microg/min)
Inclusion criteria	Type 2 diabetes; BP >90mmHg or on antihypertensives; GFR 30-100ml/min/1.73m^2
Exclusion criteria	Significant bladder dysfunction so GFR invalid; polycystic kidney disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - --: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: People with diabetes and ACR >3.0mg/mmol (Group II: UAE 30-300mg/24 hours (20-200 microg/min) n=38; Group III: UAE >300mg/24 hours (>200microg/min) n=46). 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SEM) measured GFR: Group I: enalapril: 83.38 (0.865); placebo 76.6 (1.009); Group II: enalapril 82.5 (0.786); placebo 76.3 (0.917); Group III: enalapril: 58.3 (0.896); placebo 65.3 (1.344)
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: ACE inhibitors - Enalapril. Enalapril 5mg daily, titrated to target diastolic BP 65-80mmHg or maximal daily dose of 40mg daily; achieved dose not stated. Duration 36 months . Concurrent medication/care: If patients initially on antihypertensives, drugs tapered as study drug increased; study drug used alone if possible, or if insufficient to maintain BP in target range, other drugs added (alpha- and beta-adrenergic antagonists, diuretics, calcium channel antagonists) (n=58) Intervention 2: Placebo. Placebo. Duration 36 months. Concurrent medication/care: If patients initially on antihypertensives, drugs tapered as study drug increased; study drug used alone if possible, or if insufficient to maintain BP in target range, other drugs added (alpha- and beta-adrenergic antagonists, diuretics, calcium channel antagonists)
Funding	Other (Merck Research Laboratories and Division of Research Resources of the NIH)

Study (subsidiary papers)	Lebovitz 1994-1[371] (Lebovitz 1994-2[371])
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Change in GFR per month (macroalbuminuria subgroup) at 36 months; Group 1: mean -0.533 ml/min/1.73m^2/month (SD 0.84); n=28, Group 2: mean -0.785 ml/min/1.73m^2/month (SD 1.07); n=18; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Change in GFR per month (microalbuminuria subgroup) at 36 months; Group 1: mean -0.003 ml/min/1.73m^2/month (SD 0.74); n=17, Group 2: mean -0.416 ml/min/1.73m^2/month (SD 0.88); n=21; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary protein excretion (macroalbuminuria subgroup) at 2 years; Group 1: mean 2.53 g/24 hours (SD 3.1); n=26, Group 2: mean 4.36 g/24 hours (SD 4.4); n=18; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 104: Lewis 1993

Study	Lewis 1993[383]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=409)
Countries and setting	Conducted in USA; Setting: Outpatient clinics
Line of therapy	Mixed line
Duration of study	Intervention time: Completers median 3 years (range 1.8-4.8); with endpoint (dialysis, transplantation or death) median 1.7 years (maximum 4.5); discontinued median 0.7 years (maximum 3.3)

Study	Lewis 1993[383]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary protein excretion
Stratum	CKD with diabetes: Type 1 diabetes + macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-49 years; type 1 diabetes for at least 7 years; onset before age 30; diabetic retinopathy, urinary protein excretion 500mg/24 hours or more, serum creatinine 2.5mg/dL or less; BP maintained to target without ACEI or calcium antagonists
Exclusion criteria	Pregnancy; marked departure form standard dietary recommendations; WBC <2500/mm3, congestive heart failure NYHA class III or worse; serum potassium 6mmol/L or more
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Captopril 35 (7); placebo 34 (8). Gender (M:F): 53% male. Ethnicity: White 89%; Black 7.5%; Other 3.5%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not reported; baseline urinary protein excretion: captopril: 2500 (2500) mg/d; placebo: 3000 (2600) mg/d
Indirectness of population	No indirectness
Interventions	(n=207) Intervention 1: ACE inhibitors - Captopril. 25mg three times daily. Duration Median 3 years. Concurrent medication/care: 60% on antihypertensives at baseline, of whom 62% on diuretics (range 74-87% during study), 11% on beta-blockers at baseline (15-53% during study); other drugs (e.g. labetalol, clonidine, methyldopa, prazosin, hydralazine, guanabenz, terazosin, minoxidil) proportion not stated (n=202) Intervention 2: Placebo. Placebo. Duration Median 3 years. Concurrent medication/care: 59% on antihypertensives at baseline, of whom 64% on diuretics (range 79-93% during study), 15% on beta-blockers at baseline (34-46% during study); other drugs (e.g. labetalol, clonidine, methyldopa, prazosin, hydralazine, guanabenz, terazosin, minoxidil) proportion not stated

Study	Lewis 1993[383]
Funding	Other (Public Health Service and Bristol-Myers Squibb)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: All-cause mortality at Median 3 years; Group 1: 8/205, Group 2: 14/200; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD (dialysis or transplantation) at Median 3 years; Group 1: 20/205, Group 2: 31/200; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Doubling of baseline creatinine at 4 yeas; HR 0.7 (95%CI 0.54 to 0.91) Calculated – from Kaplan Meier curve; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 105: Lewis 2001

Study (subsidiary papers)	Lewis 2001[384] (Berl 2003[67])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1148)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care

Study (subsidiary papers)	Lewis 2001[384] (Berl 2003[67])
Duration of study	Intervention time: 2.6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Proteinuria
Stratum	CKD with diabetes: Type 2 diabetes + HT + proteinuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 30-70 years; type 2 diabetes; sitting systolic BP > 135mmHg or diastolic >85mmHg or treatment with antihypertensive drugs; urinary protein excretion 900mg/24 hours or more; serum creatinine 1.0 to 3.0mg/dL in women or 1.2 to 3.0mg/dL in men
Exclusion criteria	None other
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Irbesartan 69.3 (7.1), placebo 58.3 (8.2). Gender (M:F): 68% male. Ethnicity: Non-Hispanic White 74.3%, Non-Hispanic black 12.3%, Hispanic 4.7%, Asian/Pacific Islander 4.4%, Other 4.3%
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline median (IQR) urinary protein excretion: irbesartan 2.9 (1.6-5.4) g/24 hours; placebo 2.9 (1.8-5.2) g/24 hours; baseline median (IQR) urinary albumin excretion: irbesartan 1.9 (1.0-3.8); placebo 1.9 (1.1-3.5)
Indirectness of population	No indirectness
Interventions	(n=579) Intervention 1: Angiotensin-II receptor blockers - Irbesartan. Irbesartan titrated from 75 to 300mg daily. Duration Mean 2.6 years. Concurrent medication/care: ACEI, ARB and Calcium channel blockers stopped at least 10 days before screening (BP controlled with other agents); then randomised. Antihypertensive drugs other than ACEI, ARB or calcium channel blockers used as needed for target BP: systolic <135mmHg or 10mmHg lower than at screening if screening value >145mmHg and diastolic <85mmHg. Drugs used: diuretics, beta-blockers, periphheral alpha-blockers, central alpha-2 agonists; mean 3 drugs used (n=569) Intervention 2: Placebo. Placebo. Duration Mean 2.6 years. Concurrent medication/care: ACEI, ARB and Calcium channel blockers stopped at least 10 days before screening (BP controlled with other agents); then

Study (subsidiary papers)	Lewis 2001[384] (Berl 2003[67])
	randomised. Antihypertensive drugs other than ACEI, ARB or calcium channel blockers used as needed for target BP: systolic <135mmHg or 10mmHg lower than at screening if screening value >145mmHg and diastolic <85mmHg. Drugs used: diuretics, beta-blockers, periphheral alpha-blockers, central alpha-2 agonists; mean 3.3 drugs used
Funding	Study funded by industry (Bristol-Myers Squibb and Sanofi-Aventis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IRBESARTAN versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: All-cause mortality at Mean 2.6 years; HR 0.84 (95%CI 0.63 to 1.12) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Cardiovascular mortality at Mean 2.6 years; HR 1.08 (95%CI 0.72 to 1.6) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Congestive heart failure at Mean 2.6 years; HR 0.72 (95%CI 0.52 to 1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Non-fatal myocardial infarction at Mean 2.6 years; HR 0.9 (95%CI 0.6 to 1.33) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Cerebrovascular accident at Mean 2.6 years; HR 1.01 (95%CI 0.61 to 1.67) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Cardiac revascularisation at Mean 2.6 years; HR 0.8 (95%CI 0.49 to 1.3) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: ESRD at Mean 2.6 years; HR 0.76 (95%CI 0.57 to 1.03) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum

Study (subsidiary papers)	Lewis 2001[384] (Berl 2003[67])
- Actual outcome for CKD with diabetes: Mean change in GFR at Mean 2.6 years; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Mean decrease in protein concentration at Mean 2.6 years; Group 1: mean -1.1 g/24 hours (SD 1.7); n=574, Group 2: mean -0.3 g/24 hours (SD 4.3); n=565; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 106: Li 2006

Study	Li 2006[386]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=109)
Countries and setting	Conducted in Hong Kong (China); Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Biopsy-confirmed (morphological and immunohistochemical criteria)
Stratum	CKD without diabetes: Immunoglobulin A (IgA) nephropathy
Subgroup analysis within study	Not applicable
Inclusion criteria	IgA nephropathy; age at least 18 years; proteinuria (protein at least 1g/day plus serum creatinine <2.8mg/dL) or serum creatinine 1.4-2.8mg/dL irrespective of degree of proteinuria
Exclusion criteria	Accelerated or malignant hypertension; expected survival <2 years; secondary IgA nephropathy including Henoch-Schonlein purpura; pregnant or lactating; clinically significant heaptic disease; allergy or reaction to ARBs; ACEI or ARB within 4 weeks
Recruitment/selection of patients	Not stated

Study	Li 2006[386]
Age, gender and ethnicity	Age - Mean (SD): Valsartan 40 (10); placebo 41 (9). Gender (M:F): 30/109 (28%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) eGFR: valsartan 87 (36) ml/min/1.73m^2; placebo 78 (38) ml/min/1.73m^2
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Angiotensin-II receptor blockers - Valsartan. Valsartan 80mg daily; if BP >140/90mmHg after 4 weeks, dose doubled to 160mg daily . Duration 104 weeks. Concurrent medication/care: Usual antihypertensive treatment continued; additional antihypertensives (beta-blocker [14 patients], calcium channel antagonist [19 patients] or thiazide diuretic [4 patients], followed by any appropriate additional agent [methyldopa 1 patient]) could be added at discretion of attending physicians (n=55) Intervention 2: Placebo. Placebo. Duration 104 weeks. Concurrent medication/care: Usual antihypertensive treatment continued; additional antihypertensives (beta-blocker [38 patients], calcium channel antagonist [16 patients] or thiazide diuretic [7 patients], followed by any appropriate additional agent [alpha blocker 1 pateint; methyldopa 5 patients]) could be added at discretion of attending physicians
Funding	Equipment / drugs provided by industry (Novartis Pharmaceuticals provided drugs and cost of admin support)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALSARTAN versus PLACEBO

Protocol outcome 1: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome: Doubling of serum creatinine or ESRD requiring renal replacement therapy at 2 years; HR 0.2 (95%CI 0.02 to 2) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (change in eGFR) (Critical) at 12 months minimum
- Actual outcome: GFR at 2 years; Group 1: mean 72.36 ml/min/1.73m^2 (SD 34.2); n=54, Group 2: mean 63.39 ml/min/1.73m^2 (SD 34.79); n=55; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Li 2006[386]
Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome: Proteinuria at 2 years; Group 1: mean 1.23 g/day (SD 1.25); n=54, Group 2: mean 1.97 g/day (SD 1.67); n=55; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 107: Makino 2008-1

Study (subsidiary papers)	Makino 2008-1[414] (Makino 2008-2[414])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=163)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: mean 1.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin:creatinine ratio
Stratum	CKD with diabetes: Type 2 diabetes + microalbuminuria
Subgroup analysis within study	Post-hoc subgroup analysis: Normotensive and hypertensive patients analysed separately
Inclusion criteria	Japanese; type 2 diabetes; age 30-74 years; first morning urinary albumin:creatinine ratio 100-300mg/g; serum creatinine <1.5mg/dL in males or <1.3mg/dL in females
Exclusion criteria	Type 2 diabetes before age 30; type 1 diabetes; non-diabetic renal disease; HbA1c 9% or more; seated BP 180/100mmHg or more; unstable angina, MI, CABG, PTCA, TIA or stroke in last 6 months; history of heart failure; pregnant or possibly pregnant women
Recruitment/selection of patients	not stated

Study (subsidiary papers)	Makino 2008-1[414] (Makino 2008-2[414])
Age, gender and ethnicity	Age - Mean (SD): 61.7 years. Gender (M:F): 73.1% male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: Mixed (Normotensive and hypertensive subgroups). 6. People with proteinuria :
Extra comments	Baseline GFR not reported; baseline UACR: normotensive patients: telmisartan 40mg: 173 (50.6) mg/g; telmisartan 80mg: 168 (48.6) mg/g; placebo 164 (40.3) mg/g; hypertensive: telmisartan 40mg: 172 (47.5)mg/g; telmisartan 80mg: 175 (44.6) mg/g; placebo: 178 (38.9) mg/g
Indirectness of population	No indirectness
Interventions	(n=172) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 40mg once daily. Duration Mean 1.3 years. Concurrent medication/care: Hypertensive patients continued therapy except ARBs and/or ACEI replaced by calcium channel blockers, diuretics (except potassium sparing), alpha or beta-blockers. (n=168) Intervention 2: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 80mg. Duration Mean 1.3 years. Concurrent medication/care: Hypertensive patients continued therapy except ARBs and/or ACEI replaced by calcium channel blockers, diuretics (except potassium sparing), alpha or beta-blockers. (n=174) Intervention 3: Placebo. Placebo. Duration Mean 1.3 years. Concurrent medication/care: Hypertensive patients continued therapy except ARBs and/or ACEI replaced by calcium channel blockers, diuretics (except potassium sparing), alpha or beta-blockers.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus PLACEBO

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Urinary albumin:creatinine ratio (normotensive; telmisartan 40mg) at Mean 1.3 years; Group 1: mean 136 mg/g (SD 124.3); n=58, Group 2: mean 204 mg/g (SD 140.3); n=54; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Makino 2008-1[414] (Makino 2008-2[414])
- Actual outcome for CKD with diabetes: Urinary albumin:creatinine ratio (normotensive; telmisartan 80mg) at Mean 1.3 years; Group 1: mean 112 mg/g (SD 113.7); n=51, Group 2: mean 204 mg/g (SD 140.3); n=54; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Urinary albumin:creatinine ratio (hypertensive; telmisartan 40mg) at Mean 1.3 years; Group 1: mean 134 mg/g (SD 137.5); n=114, Group 2: mean 219 mg/g (SD 180.2); n=120; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Urinary albumin:creatinine ratio (hypertensive; telmisartan 80mg) at Mean 1.3 years; Group 1: mean 113 mg/g (SD 122.1); n=117, Group 2: mean 219 mg/g (SD 180.2); n=120; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to overt nephropathy (normotensive; telmisartan 40mg) at Mean 1.3 years; Group 1: 7/58, Group 2: 18/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to overt nephropathy (normotensive; telmisartan 80mg) at Mean 1.3 years; Group 1: 5/51, Group 2: 18/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to overt nephropathy (hypertensive; telmisartan 40mg) at Mean 1.3 years; Group 1: 17/114, Group 2: 41/120; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to overt nephropathy (hypertensive; telmisartan 80mg) at Mean 1.3 years; Group 1: 13/117, Group 2: 41/120; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (normotensive; telmisartan 40mg) at Mean 1.3 years; Group 1: 9/58, Group 2: 1/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (normotensive; telmisartan 80mg) at Mean 1.3 years; Group 1: 10/51, Group 2: 1/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (hypertensive; telmisartan 40mg) at Mean 1.3 years; Group 1: 14/114, Group 2: 1/120; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (hypertensive; telmisartan 80mg) at Mean 1.3 years; Group 1: 25/117, Group 2: 1/120; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 108: Mann 2001

Study	Mann 2001[416]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=980)
Countries and setting	Conducted in Canada, Germany; Setting: Outpatient clinics
Line of therapy	Unclear
Duration of study	Intervention time: Median 4.5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum creatinine
Stratum	Overall: Renal insufficiency (serum creatinine 1.4mg/dL or more), with or without diabetes
Subgroup analysis within study	Post-hoc subgroup analysis: Renal insufficiency (serum creatinine 1.4mg/dL or more) or no renal insufficiency
Inclusion criteria	Age at least 55 years; vascular disease or diabetes plus another cardiovascular risk factor
Exclusion criteria	Heart failure, intolerance of ACEI or vitamin E, serum creatinine >2.3mg/dL, dipstick positive proteinuria >1+
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Ramipril 68.1 (6.6); placebo 68.8 (7.2). Gender (M:F): 87.2% male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline median (IQR) albumin:creatinine ratio ramipril: 0.73 (0.26-2.81) mg/mmol; placebo 0.77 (0.22-2.89) mg/mmol
Indirectness of population	No indirectness
Interventions	(n=509) Intervention 1: ACE inhibitors - Ramipril. Ramipril 10mg/d. Duration Median 4.5 years. Concurrent medication/care: Antiplatelet agents: 80.8%; beta-blockers: 48.1%; calcium antagonists: 55.6%; diuretics: 22.2%; cholesterol lowering drugs: 29.7% (n=471) Intervention 2: Placebo. Placebo. Duration Median 4.5 years. Concurrent medication/care: Antiplatelet agents: 81.1%; beta-blockers: 47.6%; calcium antagonists: 51.8%; diuretics: 25.3%; cholesterol lowering drugs: 29.5%

Study	Mann 2001[416]
Funding	Other (Medical Research Council of Caanada, Ontario Heart Foundation, Aventis, Astra-Zeneca, NEGMA, Natural Source Vitamin E Producers Association)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome: Cardiovascular mortality at 4.5 years; HR 0.59 (95%CI 0.39 to 0.91) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality at 4.5 years; HR 0.59 (95%CI 0.42 to 0.83) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome: Fatal or non-fatal MI at 4.5 years; HR 0.78 (95%CI 0.54 to 1.11) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Stroke at 4.5 years; HR 0.83 (95%CI 0.44 to 1.56) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Revascularisation at 4.5 years; HR 0.96 (95%CI 0.7 to 1.33) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Hospitalisation (Important) at 12 months minimum - Actual outcome: Hospitalisation for heart failure at 4.5 years; HR 0.56 (95%CI 0.3 to 1.06) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 109: Marre 2004

Study	Marre 2004[425]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4912)

Study	Marre 2004[425]
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 47 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + micro- or macro-albuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Older than 50 years; type 2 diabetes; urinary albumin excretion 20mg/L or more in 2 successive random urine samples
Exclusion criteria	Serum creatinine >150microg/L; treatment with insulin, ACEI or ARB; congestive chronic heart failure; MI in last 3 months; urinary tract infection; previous intolerance to ACEI
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Ramipril 65.2 (8.4); placebo 65.0 (8.3). Gender (M:F): 3432/4912 (70%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Mean eGFR not reported; 74% microalbuminuria; 26% proteinuria
Indirectness of population	No indirectness
Interventions	(n=2443) Intervention 1: ACE inhibitors - Ramipril. Ramipril 1.25mg once daily, usually in the mornings. Duration Median 47 months. Concurrent medication/care: Antihypertensives 47.4%; lipid lowering agents 29.8%; antiplatelets 18.3% (n=2469) Intervention 2: Placebo. Placebo. Duration Median 47 months. Concurrent medication/care: Antihypertensives 48.0%; lipid lowering agents 27.3%; antiplatelets 19.1%
Funding	Other (Aventis (Paris) and Programme Hospitalier de Recherche Clinique (French Health Ministry))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO	

Study	Marre 2004[425]
	Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Cardiovascular mortality at 47 months; Group 1: 141/2443, Group 2: 133/2469; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: All-cause mortality at 47 months; Group 1: 334/2443, Group 2: 324/2469; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Non-fatal myocardial infarction at 47 months; Group 1: 52/2443, Group 2: 59/2469; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Non-fatal stroke at 47 months; Group 1: 89/2443, Group 2: 84/2469; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Heart failure requiring hospital admission or intervention of mobile coronary care unit at 47 months; Group 1: 76/2443, Group 2: 91/2469; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Revascularisation (cardiac or peripheral) at 47 months; Group 1: 179/2443, Group 2: 201/2469; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: End stage renal failure at 47 months; Group 1: 4/2443, Group 2: 10/2469; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 110: Matsuda 2003

Study	Matsuda 2003[431]

Study	Matsuda 2003[431]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=62)
Countries and setting	Conducted in Japan; Setting: Outpatient centres
Line of therapy	Unclear
Duration of study	Intervention time: 96 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary protein excretion
Stratum	CKD without diabetes: HT + proteinuria (diabetes excluded)
Subgroup analysis within study	Not applicable
Inclusion criteria	Hypertension (>140/90mmHg); proteinuria (>0.5g/day); serum creatinine level <265 micromol/L; creatinine clearance >30ml/min/1.72 m^2
Exclusion criteria	Diabetic nephropathy, polycystic kidney disease, chronic pyelonephritis
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: Mean (SEM): perindopril 51 (4); trandolapril 50 (5); candesartan 58 (5); losartan 51 (3). Gender (M:F): 33/62 (53%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Mean GFR not reported; mean (SEM) urinary protein excretion: perindopril 2.7 (0.5) g/d; trandolapril 2.7 (0.5) g/d; candesartan 3.0 (0.6) g/d; losartan 2.5 (0.4) g/d
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: ACE inhibitors - Perindopril. Perinodpril 2mg/d, titrated to acheive BP <135/85mmHg; final dose not stated. Duration 96 weeks. Concurrent medication/care: Some (14/62 in total but not shown by treatment group) had anitplatelet therapy (dipyridamole or dilazep dihydrochloride) (n=15) Intervention 2: ACE inhibitors - Trandolapril. Trandolapril 0.5mg/d, titrated to achieve BP < 135/85mmHg; final dose not stated. Duration 96 weeks. Concurrent medication/care: Some (14/62 in total but not shown by treatment

Study	Matsuda 2003[431]
	group) had anitplatelet therapy (dipyridamole or dilazep dihydrochloride) (n=15) Intervention 3: Angiotensin-II receptor blockers - Losartan. Losartan 25ng/d, titrated to achieve BP <135/85mmHg; final dose not stated. Duration 96 weeks. Concurrent medication/care: Some (14/62 in total but not shown by treatment group) had anitplatelet therapy (dipyridamole or dilazep dihydrochloride) (n=17) Intervention 4: Angiotensin-II receptor blockers - Candesartan. Candesartan cilexetil 4mg/d, titrated to achieve BP < 135/85mmHg; final dose not stated. Duration 96 weeks. Concurrent medication/care: Some (14/62 in total but not shown by treatment group) had anitplatelet therapy (dipyridamole or dilazep dihydrochloride)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL versus TRANDOLAPRIL

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -60 % (SD 27.1); n=15, Group 2: mean -53 % (SD 27.1); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL versus LOSARTAN

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -60 % (SD 27.1); n=15, Group 2: mean -36 % (SD 15.5); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL versus CANDESARTAN

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -60 % (SD 27.1); n=15, Group 2: mean -49 % (SD 20.6); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Matsuda 2003[431]
	RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANDOLAPRIL versus LOSARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -53 (SD 27.1); n=15, Group 2: mean -36 (SD 15.5); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANDOLAPRIL versus CANDESARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -53 % (SD 27.1); n=15, Group 2: mean -49 % (SD 20.6); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus LOSARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Change in proteinuria (%) at 96 weeks; Group 1: mean -49 (SD 20.6); n=17, Group 2: mean -36 (SD 15.5); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 111: Muirhead 1999

Study	Muirhead 1999[459]

Study	Muirhead 1999[459]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in Canada; Setting: Outpatient clinics
Line of therapy	Mixed line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes and "incipient diabetic nephropathy": albumin excretion rate 20-300 microg/min with GFR 60ml/min/1.73m^2
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older; type 2 diabetes; "incipient diabetic nephropathy": albumin excretion rate 20-300 microg/min with GFR 60ml/min/1.73m^2; sitting BP 160/95mmHg or less (treated or untreated); women of childbearing potential included if using effective birth control not based on combined oestrogen/progestogen; if on ACE or calcium channel blockers, these had to be discontinued for 28 days before randomisation
Exclusion criteria	"Brittle" diabetes (i.e. increased risk of hypoglycaemia) or history of non-compliance
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Valsartan 80mg 53.7 (9.5); valsartan 160mg 58.3 (9.5); captopril 56.7 (10.0); placebo 55.5 (11.3). Gender (M:F): 89/122 (73%) male. Ethnicity: 90% White; 1% Black; 4% Asian; 5% Other
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline geometric mean measured GFR: valsartan 80mg 101.5ml/min/1.73m^2; valsartan 180mg 83.1; captopril 88.1; placebo 86.7
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Angiotensin-II receptor blockers - Valsartan. Valsartan 80mg once daily. Duration 52 weeks. Concurrent medication/care: Glycaemic control maintained with patient's usual treatment; use of antihypertensives (except diuretics or beta-blockers), oestrogen replacement therapy or thyroid medication <6 months before trial entry

Study	Muirhead 1999[459]
	was prohibited. 32.3% taking antihypertensives during trial. (n=31) Intervention 2: Angiotensin-II receptor blockers - Valsartan. Valsartan 180mg once daily. Duration 52 weeks. Concurrent medication/care: Glycaemic control maintained with patient's usual treatment; use of antihypertensives (except diuretics or beta-blockers), oestrogen replacement therapy or thyroid medication <6 months before trial entry was prohibited. 29.0% taking antihypertensives during trial. (n=29) Intervention 3: ACE inhibitors - Captopril. Captopril 25mg three times daily. Duration 52 weeks. Concurrent medication/care: Glycaemic control maintained with patient's usual treatment; use of antihypertensives (except diuretics or beta-blockers), oestrogen replacement therapy or thyroid medication <6 months before trial entry was prohibited. 37.9% taking antihypertensives during trial. (n=31) Intervention 4: Placebo. Placebo. Duration 52 weeks. Concurrent medication/care: Glycaemic control maintained with patient's usual treatment; use of antihypertensives (except diuretics or beta-blockers), oestrogen replacement therapy or thyroid medication <6 months before trial entry was prohibited. 54.8% taking antihypertensives during trial.
Funding	Study funded by industry (Novartis Pharma AG, Basel, Switzerland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALSARTAN versus CAPTOPRIL

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Progression to clinical proteinuria at 52 weeks; Group 1: 1/31, Group 2: 1/29; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALSARTAN versus PLACEBO

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Progression to clinical proteinuria at 52 weeks; Group 1: 1/31, Group 2: 3/31; Risk of bias: Low; Indirectness of outcome: No

Study	Muirhead 1999[459]
indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression to clinical proteinuria at 52 weeks; Group 1: 1/29, Group 2: 3/31; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 112: Nakamura 2010

Study	Nakamura 2010[467]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Renal biopsy, clinical history
Stratum	CKD without diabetes: Non-diabetic CKD + HT
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-diabetic CKD (diagnosed by renal biopsy and/or clinical history) with mild renal insufficiency; hypertension

Study	Nakamura 2010[467]
Exclusion criteria	Clinical or laboratory evidence of underlying systemic disease including collagen disease or liver disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Telmisartan 35 (7); enalapril 36 (8). Gender (M:F): 20/30 (67%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Mean eGFR (modified MDRD formula) 80ml/min
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 80mg once daily. Duration 12 months. Concurrent medication/care: Patients on antihypertensive therapy kept at same doses except ACEI or ARB withdrawn. Diuretics 7/15; calcium antagonist 10/15; alpha blocker 4/15; beta blocker 2/15; other 3/15; statin 7/15; antiplatelet 11/15; allopurinol 3/15; steroid 3/15. (n=15) Intervention 2: ACE inhibitors - Enalapril. Enalapril 10mg once daily. Duration 12 months . Concurrent medication/care: Patients on antihypertensive therapy kept at same doses except ACEI or ARB withdrawn. Diuretics 7/15; calcium antagonist 9/15; alpha blocker 4/15; beta blocker 2/15; other 2/15; statin 8/15; antiplatelet 12/15; allopurinol 4/15; steroid 3/15.
Funding	Funding not stated
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 113: Nakamura 2010

Study	Nakamura 2010[468]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Japan; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes + HT + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 2 diabetes + HT (BP > 140/90mmHg despite antihypertensive drugs [not ACEI or ARB])+ microalbuminuria
Exclusion criteria	Serum creatinine >1.2mg/dL or 24 hour creatinine clearance <80ml/min; malignancy, heart disease, cerebrovascular disease, liver disease or systemic disease (e.g. collagen disease)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 54 (13). Gender (M:F): 38/68 (56%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Mean GFR not stated; urinary albumin excretion: losartan 109.8 (42.9); candesartan 104.0 (42.4); olmesartan 104.2 (45.0); telmisartan 108.7 (32.6) microg/min
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Angiotensin-II receptor blockers - Losartan. Losartan 100mg/d. Duration 12 months. Concurrent medication/care: Other antihypertensive drugs (except ACEI) could be added to attain target BP <130/80mmHg. Calcium channel blocker 41.2%, alpha blocker 23.5%; diuretic 47.1%; other antihypertensive 17.6%; insulin 29.4%; pioglitazone 35.3%; voglibose 23.5%; glibenclamide 35.3%; antiplatelet 29.4%; statin 35.3%

Study	Nakamura 2010[468]
	(n=17) Intervention 2: Angiotensin-II receptor blockers - Candesartan. Candesartan 12mg/d. Duration 12 months. Concurrent medication/care: Other antihypertensive drugs (except ACEI) could be added to attain target BP <130/80mmHg. Calcium channel blocker 35.3%, alpha blocker 23.5%; diuretic 47.1%; other antihypertensive 17.6%; insulin 23.5%; pioglitazone 29.4%; voglibose 29.4%; glibenclamide 41.2%; antiplatelet 29.4%; statin 41.2% (n=17) Intervention 3: Angiotensin-II receptor blockers - Olmesartan. Olmesartan 40mg/d. Duration 12 months. Concurrent medication/care: Other antihypertensive drugs (except ACEI) could be added to attain target BP <130/80mmHg. Calcium channel blocker 41.2%, alpha blocker 17.6%; diuretic 41.2%; other antihypertensive 23.5%; insulin 29.4%; pioglitazone 29.4%; voglibose 23.5%; glibenclamide 41.2%; antiplatelet 23.5%; statin 35.3% (n=17) Intervention 4: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 80mg/d. Duration 12 months. Concurrent medication/care: Other antihypertensive drugs (except ACEI) could be added to attain target BP <130/80mmHg. Calcium channel blocker 35.3%, alpha blocker 17.6%; diuretic 41.2%; other antihypertensive 17.6%; insulin 23.5%; pioglitazone 29.4%; voglibose 29.4%; glibenclamide 35.3%; antiplatelet 23.5%; statin 35.3%
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus OLMESARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion at 12 months; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 114: Nankervis 1998

Study	Nankervis 1998[470]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Australia; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 1 or type 2 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-insulin dependent or insulin-dependent diabetes; age 18-65 years; microalbuminuria (urinary albumin excretion 20-200mg/L); stable glycaemic control; normotensive or hypertensive
Exclusion criteria	Non-diabetic renal disease or other major disease; previous treatment with ACEI
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: Mean (SEM) perindopril 43 (3); placebo 49 (3). Gender (M:F): 32/40 (80%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SEM) measured GFR: perindopril 91 (7); placebo 96 (8)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: ACE inhibitors - Perindopril. Perindopril 4mg once daily. Duration 3 years. Concurrent medication/care: If BP became or remained elevated, other antihypertensive medication added: 10 patients received calcium channel blockers, beta blockers, alpha blockers or diuretics (n=20) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: If BP became or remained elevated, other antihypertensive medication added: 7 patients received calcium channel blockers, beta blockers,

Study	Nankervis 1998[470]
	alpha blockers or diuretics
Funding	Study funded by industry (Servier Laboratories Australia)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: GFR at 3 years; Group 1: mean 82 ml/min (SD 33); n=17, Group 2: mean 90 ml/min (SD 26.2); n=14; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 3 years; Group 1: mean 3.2 microg/min (natural log) (SD 3.4); n=17, Group 2: mean 4.8 microg/min (natural log) (SD 2.5); n=14; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 115: O'hare 2000

Study	O'hare 2000[502]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=134)
Countries and setting	Conducted in Irish Republic, United Kingdom; Setting: Outpatient clinics
Line of therapy	1st line
Duration of study	Intervention time: 2 years

Study	O'hare 2000[502]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 1 diabetes; microalbuminuria (AER 20-200microg/min in 2 of 3 collections); untreated BP <150/90mmHg for patients under 50 years and <165/90mmHg for patients 50-65 years
Exclusion criteria	Pregnant or lactating; women of childbearing potential not using adequate contraception; concomitant therapy for hypertension; NSAIDs; history of drug or alcohol abuse; other known renal disease or raised creatinine levels (>120micromol/L) or liver function tests twice that of normal on repeat testing; iodine sensitivity (unable to participate in GFR measurements)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Ramipril 5mg: 40 (13); ramipril 1.25mg: 40 (11); placebo 40 (12). Gender (M:F): 95/134 (71%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (SD) measured GFR: ramipril 5mg: 109 (29); ramipril 1.25mg: 104 (26); placebo 100 (23) ml/min
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: ACE inhibitors - Ramipril. Ramipril 5mg . Duration 2 years. Concurrent medication/care: None stated (n=44) Intervention 2: ACE inhibitors - Ramipril. Ramipril 1.25mg. Duration 2 years. Concurrent medication/care: None stated (n=46) Intervention 3: Placebo. Placebo. Duration 2 years. Concurrent medication/care: None stated
Funding	Study funded by industry (Hoechst Marion Rousel (Aventis))

Study	O'hare 2000[502]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO Protocol outcome 1: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Myocardial infarction (ramipril 5mg) at 2 years; Group 1: 1/44, Group 2: 1/46; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Myocardial infarction (ramipril 1.25mg) at 2 years; Group 1: 2/44, Group 2: 1/46; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression to macroalbuminuria (ramipril 5mg) at 2 years; Group 1: 4/44, Group 2: 5/46; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Progression to macroalbuminuria (ramipril 1.25mg) at 2 years; Group 1: 2/44, Group 2: 5/46; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (ramipril 5mg) at 2 years; Group 1: 9/44, Group 2: 2/46; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria (ramipril 1.25mg) at 2 years; Group 1: 5/44, Group 2: 2/46; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 116: Parving 2001

Study	Parving 2001[527]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=590)

Study	Parving 2001[527]
Countries and setting	Conducted in Multiple countries; Setting: Outpatient clinics
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + HT + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 30-70 years; hypertension (2 of 3 BP readings 1 week apart >135/85mmHg); type 2 diabetes; albumin excretion rate 20-200microg/min in 2 of 3 consecutive sterile overnight urine samples; serum creatinine no more than 1.5mg/dL for men or 1.1mg/dL for women
Exclusion criteria	Non-diabetic kidney disease, cancer, life-threatening disease with death expected within 2 years, indication for ACEI or ARB
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 300mg irbesartan 57.3 (7.9); 150mg irbesartan 58.4 (8); placebo 58.3 (8.7). Gender (M:F): 404/590 (68%) male. Ethnicity: White: 300mg irbesartan 96.4%; 150mg irbesartan 97.4%; placebo 98.0%; the rest non-white
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Indirectness of population	No indirectness
Interventions	(n=194) Intervention 1: Angiotensin-II receptor blockers - Irbesartan. Irbesartan 300mg daily (increased to target level in two stages lasting 2 weeks each). Duration 2 years. Concurrent medication/care: Single-blind 3 week run in period during which antihypertensive treatments stopped and replaced by placebo. By end of study, 43.3% on any antihypertensive drugs (19.1% diuretics, 13.4% beta-blockers, 23.2% calcium channel blockers, 17.5% other). Glucose lowering: diet 12.4%, oral antidiabetic drugs 54.6%, insulin + oral 16.5%, insulin alone 16.5%). Lipid lowering drugs: any 24.2%, statin alone 14.9%, fibrate alone 7.2%, statin and fibrate 2.1%. Aspirin (325mg daily or less) 16.5%. (n=195) Intervention 2: Angiotensin-II receptor blockers - Irbesartan. Irbesartan 300mg daily (increased to target level in two stages lasting 2 weeks each). Duration 2 years. Concurrent medication/care: Single-blind 3 week run in period

Study	Parving 2001[527]
	during which antihypertensive treatments stopped and replaced by placebo. By end of study, 45.1% on any antihypertensive drugs (21.5% diuretics, 13.8% beta-blockers, 17.9% calcium channel blockers, 11.3% other). Glucose lowering: diet 10.8%, oral antidiabetic drugs 51.8%, insulin + oral 19.0%, insulin alone 18.5%). Lipid lowering drugs: any 26.7%, statin alone 19.0%, fibrate alone 5.6%, statin and fibrate 2.1%. Aspirin (325mg daily or less) 21.5%. (n=201) Intervention 3: Placebo. Placebo. Duration 2 years. Concurrent medication/care: Single-blind 3 week run in period during which antihypertensive treatments stopped and replaced by placebo. By end of study, 56.2% on any antihypertensive drugs (25.4% diuretics, 18.9% beta-blockers, 27.4% calcium channel blockers, 14.9% other). Glucose lowering: diet 10.4%, oral antidiabetic drugs 45.8%, insulin + oral 17.4%, insulin alone 26.4%). Lipid lowering drugs: any 25.9%, statin alone 18.9%, fibrate alone 6.0%, statin and fibrate 1.0%. Aspirin (325mg daily or less) 14.4%.
Funding	Study funded by industry (Sanofi-Synthelabo and Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IRBESARTAN versus PLACEBO

Protocol outcome 1: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Non-fatal cardiovascular events (irbesartan 300mg) at 2 years; Group 1: 9/194, Group 2: 17/201; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Progression to macroalbuminuria (irbesartan 300mg) at 2 years; Group 1: 10/194, Group 2: 30/201; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Progression to macroalbuminuria (irbesartan 150mg) at 2 years; Group 1: 19/195, Group 2: 30/201; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Regression to normoalbuminuria (irbesartan 300mg) at 2 years; Group 1: 66/194, Group 2: 42/201; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Regression to normoalbuminuria (irbesartan 150mg) at 2 years; Group 1: 47/195, Group 2: 42/201; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Parving 2001[527]
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 117: Parving 2012

Study	Parving 2012[531]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=8606)
Countries and setting	
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 32.9 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: MDRD equation
Stratum	CKD with diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	35 years old or older, with type II diabetes and evidence of microalbuminuria, macroalbuminuria or cardiovascular disease concomitant treatment must include an ACE inhibitor or an ARB.
Exclusion criteria	Serum potassium >5.0 mmol/L. History of any cardiovascular event (stroke, transient ischemic cerebral attack, MI, unstable angina, CABG, PCI, hospitalization due to HF) during the 3 months prior. Untreated hypertension. Second or third degree heart block without a pacemaker. Clinically significant valvular heart disease. Renal artery stenosis. Type I diabetes.
Recruitment/selection of patients	4-12 week screening period to confirm eligibility.
Age, gender and ethnicity	Age - Mean (SD): 64.5+/-9.7. Gender (M:F): 68% male, 32% female. Ethnicity: 57% caucasian, 3.25% black, 31.7% Asian, 8% other.

Study	Parving 2012[531]
Further population details	1. Black and minority ethnic groups: Mixed 2. Older people aged 75 or over: Not applicable / Not stated / Unclear 3. People with cardiovascular disease: Mixed (People at high risk of cardiovascular disease.). 4. People with diabetes and proteinuria: People with diabetes and ACR >3.0mg/mmol (All participants had diabetes and micro or macroalbuminuria). 5. People with hypertension: Blood pressure <140/90mmHg (Treated hypertension allowed.). 6. People with proteinuria : ACR 3-30 mg/mmol (Mean at baseline 206mg/g (20.6 mg/mmol)).
Extra comments	At baseline, mean systolic blood pressure: 137/74, eGFR: 57ml/min/1.73m^2, ACR: 207mg/g.
Indirectness of population	No indirectness: 98% of participants had CKD
Interventions	(n=4274) Intervention 1: Direct renin inhibitors - Aliskiren. 150mg once daily, increased to 300mg at 4 weeks. Duration Median 32.9 months. Concurrent medication/care: Concommitent treatment must include either an ACE inhibitor or an ARB. (n=4287) Intervention 2: Placebo. Placebo. Duration Median 32.9 months. Concurrent medication/care: Concomitant treatment must include either an ACE inhibitor or an ARB
Funding	Study funded by industry (Novartis.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALISKIREN versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: All-cause mortality at Median 32.9 years; HR 1.06 (95%CI 0.92 to 1.23) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Cardiovascular mortality at Median 32.9 months; HR 1.16 (95%CI 0.96 to 1.39) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Cardiac arrest with resuscitation at Median 32.9 months; HR 2.4 (95%CI 1.05 to 5.48) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Myocardial infarction (fatal or non-fatal) at Median 32.9 months; HR 1.04 (95%CI 0.83 to 1.31) Reported; Risk of bias: Low;

Study	Parving 2012[531]
Indirectness of outcome: Serious indirectness - Actual outcome for CKD with diabetes: Stroke (fatal or nonfatal) at Median 32.9 months; HR 1.22 (95%CI 0.96 to 1.55) Reported; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD, death attributable to kidney failure, or loss of kidney function (need for RRT with no dialysis or transplant available or initiated). at Median 32.9 months; HR 1.08 (95%CI 0.84 to 1.4) Reported; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 4: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Doubling of baseline serum creatinine at Median 32.9 months; HR 0.97 (95%CI 0.8 to 1.17) Reported; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 5: Hospitalisation (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Unplanned hospitalisation for heart failure at Median 32.9 months; HR 0.95 (95%CI 0.78 to 1.14) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 118: Penno 1998

Study	Penno 1998[538]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient clinics
Line of therapy	Unclear
Duration of study	Intervention time: 2 years

Study	Penno 1998[538]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 1 diabetes + microalbuminuria
Subgroup analysis within study	Post-hoc subgroup analysis: Microalbuminuria
Inclusion criteria	Non-hypertensive (diastolic BP 75-90mmHg; systolic 155mmHg or less); type 1 diabetes; age 20-59 years
Exclusion criteria	None other
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: 20-59 years. Gender (M:F): 308/530 (58%) male in whole study (not shown for subgroup). Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: Mixed (Microalbuminuria subgroup; all type 1 diabetes). 5. People with hypertension: 6. People with proteinuria :
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: ACE inhibitors - Lisinopril. Lisinopril 10mg; at 3 months, dose could be increased to 20mg if diastolic BP did not fall below target level of 75mmHg.. Duration 2 years. Concurrent medication/care: Not stated (n=34) Intervention 2: Placebo. Placebo. Duration 2 years. Concurrent medication/care: Not stated
Funding	Study funded by industry (Zeneca Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL versus PLACEBO

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Progression to macroalbuminuria at 2 years; Group 1: 3/41, Group 2: 6/34; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Regression to normoalbuminuria at 2 years; Group 1: 19/41, Group 2: 11/34; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study	Penno 1998[538]
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 119: PREVEND IT trial: Asselbergs 2004

Study	PREVEND IT trial: Asselbergs 2004[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=864)
Countries and setting	Conducted in Netherlands; Setting: Outpatient clinics.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 24 hour urinary albumin excertion
Stratum	CKD without diabetes: 2.55% had diabetes melitus
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent microalbuminuria (>10mg/L in 1 early morning sample and 15-300 mg/24 hours in 2 24 hour urine samples), blood pressure <160/100 mmHg and no use of antihypertensive medication, total cholesterol level <8mmol/L or <5mmol/L in case of previous myocardial infarction, no use of lipid lowering medication.
Exclusion criteria	Creatinine clearance <60^ of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptior antagonists.
Recruitment/selection of patients	Questionnaire sent to all inhibitants of Groningen, of those that replied all who met the inclusion citeria were invited to an outpaithe appointment to confirm inclusion criteria and for randomisation.

Study	PREVEND IT trial: Asselbergs 2004[42]
Age, gender and ethnicity	Age - Mean (SD): Placebo: 51.5 (11.4), Fosinopril: 51.1 (12.2). Gender (M:F): 64.9% male. Ethnicity: 96% white
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear (Only states 96% white.). 2. Older people aged 75 or over: Not applicable / Not stated / Unclear 3. People with cardiovascular disease: People without cardiovascular disease (People at increased risk of cardiovascular disease). 4. People with diabetes and proteinuria: 5. People with hypertension: Blood pressure <140/90mmHg (Cut off was 160/100mmHg). 6. People with proteinuria : ACR >30 mg/mmol (15-300mg/mmol).
Extra comments	Study is a 2x2 factorial design also including pravastatin. Pravastatin results not reported here (not in protocol). Compliance considered as >75% of supplied study medication being taken.
Indirectness of population	No indirectness
Interventions	(n=433) Intervention 1: Placebo. Placebo. Duration 4 years. Concurrent medication/care: 5.2% received an open label ACE inhibitor and 3.5% received open-label statin as prescribed by their general pysicians (not stated which treatment arm). (n=431) Intervention 2: ACE inhibitors - Fosinopril. 20mg. Duration 4 years. Concurrent medication/care: 5.2% received an open label ACE inhibitor and 3.5% received open-label statin as prescribed by their general pysicians (not stated which treatment arm).
Funding	Study funded by industry (Unrestricted grant rom Bristol-Myers Squibb and grants from the Dutch kidney Foundation an Netherlands Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PLACEBO versus FOSINOPRIL

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome for CKD without diabetes: Cardiovascular mortality and hospitalisation for carvdioascular morbidity. at Mean 46+7 months; HR 0.6 (95%CI 0.33 to 1.1) Reported; Risk of bias: Low; Indirectness of outcome: Serious indirectness
- Actual outcome for CKD without diabetes: Cardiovascular mortality at 4 years; Group 1: 3/433, Group 2: 5/431; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Study	PREVEND IT trial: Asselbergs 2004[42]
Protocol outcome 2: Hospitalisation (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Hospitalisation for non-fatal myocardial infarction, heart failure, peripheral vascular disease or cerebroascular accident. at 4 years; Group 1: 25/433, Group 2: 14/431; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Median urinary albumin excretion (mg/24 hours) Final values at 4 years; Other: Placebo: 23.2 (13.4-42.6), Fosinopril: 18.6 (11.0-39.9); Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 120: Ravid 1993

Study	Ravid 1993[566]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in Israel; Setting: Outpatient clinics
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 2 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Age < 50 years; Duration of type 2 diabetes < 10 years ; BMI <27kg/m^2; normal BP on 2 occasions (140/90mmHg or

Study	Ravid 1993[566]
	less, mean BP <107mmHg); serum creatinine <1.4mg/dL; urinary protein excretion 30-300 mg/24 hours on 2 visits without evidence of urinary tract infection
Exclusion criteria	Systemic, renal, cardiac or hepatic disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Enalapril 43.5 (3); placebo 44.8 (3.5). Gender (M:F): 42/94 (45%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: ACE inhibitors - Enalapril. Enalapril 10mg daily. Duration 5 years. Concurrent medication/care: Overall, 16 patients received insulin, 43 oral antidiabetic drugs, 49 diet for diabetes (not shown by intervention/control group). (n=52) Intervention 2: Placebo. Placebo. Duration 5 years. Concurrent medication/care: Overall, 16 patients received insulin, 43 oral antidiabetic drugs, 49 diet for diabetes (not shown by intervention/control group).
Funding	Other (Nissenson-Tyomkin medical research grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression to macroalbuminuria at 5 years; Group 1: 6/49, Group 2: 19/45; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Urinary albumin excretion at 5 years; Group 1: mean 140 mg/24 hours (SD 104); n=49, Group 2: mean 310 mg/24 hours (SD 167); n=45; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12

Study	Ravid 1993[566]
	months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 121: Shen 2012

Study	Shen 2012[629]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=238)
Countries and setting	Conducted in China; Setting: Outpatient clinics
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR (modified MDRD formula)
Stratum	CKD without diabetes: eGFR 30-59ml/min/1.73m^2
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-70 years; stage 3 CKD (either eGFR <60ml/min/1.73m^2 or kidney damage for >3 months, biopsy proven or with clear clinical presentation); eGFR 39059ml/min/1.73m^2; BP 140/90mmHg or less; mean arterial pressure <107mmHg; persistent stable non-nephrotic proteinuria (0.5-2.5g/dL)
Exclusion criteria	BP > 140/90mmHg; secondary hypertension; rapidly deteriorating renal function (increase >50% serum creatinine in last 6 months): type 1 or type 2 diabetes; active infection; chronic liver disease; renal allografts; ACEI or ARB initiated for known renal disorders; patients on diuretics, steroids, immunosuppressive therapy or toehr medications
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 49.8 (11.2). Gender (M:F): 114/226 (50%) male. Ethnicity: All Chinese
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :

Study	Shen 2012[629]
Extra comments	Baseline eGFR losartan: 44.8 (8.1); placebo 44.5 (8.5)
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: Angiotensin-II receptor blockers - Losartan. Losartan 50mg once daily in the morning. Duration 12 months. Concurrent medication/care: ACEI or ARB washed out for 1 month; 2 week washout for other drugs (n=119) Intervention 2: Placebo. Placebo. Duration 12 months. Concurrent medication/care: ACEI or ARB washed out for 1 month; 2 week washout for other drugs
Funding	Academic or government funding (Several government grants, China)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: eGFR at 12 months; Group 1: mean 44.1 ml/min/1.73m^2 (SD 7.7); n=112, Group 2: mean 39.1 ml/min/1.73m^2 (SD 7.4); n=114; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Proteinuria at 12 months; Group 1: mean 0.99 g/d (SD 0.48); n=112, Group 2: mean 1.64 g/d (SD 0.5); n=114; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Regression to normoalbuminuria at 12 months; Group 1: 16/112, Group 2: 0/114; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 122: Solomon 2006

Study	Solomon 2006[643]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1355)
Countries and setting	Conducted in Unknown; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 4.8 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR by 4-variable MDRD formula
Stratum	Overall: CKD (eGFR < 60ml/min/1.73m^2) with or without diabetes
Subgroup analysis within study	Post-hoc subgroup analysis: eGFR <45ml/min/1.73m^2 or 45-59.9 ml/min/1.73m^2 (or 60-74.9 ml/min/1.73m^2 or 75 ml/min/1.73m^2 or more)
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): eGFR <45 ml/min/1.73m^2: 70.2 (7.9); eGFR 45-59.9 ml/min/1.73m^2: 68.0 (7.7). Gender (M:F): Define. Ethnicity: 95% white
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: People with cardiovascular disease (Stable coronary artery disease + reduced GFR). 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	1355 patients had reduced eGFR out of total 8280 in trial (157 had eGFR <45 ml/min/1.73m^2 and 1198 had eGFR 45-59.9 ml/min/1.73m^2)
Indirectness of population	No indirectness
Interventions	(n=698) Intervention 1: ACE inhibitors - Trandolapril. Trandolapril target dose 4mg/d; achieved dose not stated. Duration 4.8 years. Concurrent medication/care: eGFR <45 ml/min/1.73m^2 (not stated by treatment subgroup): calcium channel blocker 50.3%; beta-blocker 63.1%; aspirin/antiplatelet 84.7%; lipid lowering drug 66.2%; diuretic

Study	Solomon 2006[643]
	31.8%; HRT 14.0%. eGFR 45-59.9 ml/min/1.73m^2: calcium channel blocker 38.3%; beta-blocker 61.5%; aspirin/antiplatelet 90.6%; lipid lowering drug 68.5%; diuretic 20.5%; HRT 7.8% Comments: 79 eGFR <45 ml/min/1.73m^2 + 619 eGFR 45-59.9 ml/min/1.73m^2 (n=657) Intervention 2: Placebo. Placebo. Duration 4.8 years. Concurrent medication/care: eGFR <45 ml/min/1.73m^2 (not stated by treatment subgroup): calcium channel blocker 50.3%; beta-blocker 63.1%; aspirin/antiplatelet 84.7%; lipid lowering drug 66.2%; diuretic 31.8%; HRT 14.0%. eGFR 45-59.9 ml/min/1.73m^2: calcium channel blocker 38.3%; beta-blocker 61.5%; aspirin/antiplatelet 90.6%; lipid lowering drug 68.5%; diuretic 20.5%; HRT 7.8% Comments: 78 eGFR <45 ml/min/1.73m^2 + 579 eGFR 45-59.9 ml/min/1.73m^2
Funding	Other (National Heart, Lung, and Blood Institute and Knoll Pharmaceuticals and Abbott Laboratories)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANDOLAPRIL versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome: All-cause mortality (eGFR 45-59.9 ml/min/1.73m^2) at 4.8 years; Group 1: 56/619, Group 2: 72/579; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Cardiovascular mortality (eGFR <45 ml/min/1.73m^2) at 4.8 years; Group 1: 11/79, Group 2: 14/78; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Cardiovascular mortality (eGFR 45-59.9 ml/min/1.73m^2) at 4.8 years; Group 1: 28/619, Group 2: 36/579; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality (eGFR <45ml/min/1.73m^2) at 4.8 years; Group 1: 13/79, Group 2: 20/78; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health

Study	Solomon 2006[643]
	related quality of life (Important) at 12 months minimum

Table 123: Tobe 2011-2

Study (subsidiary papers)	Tobe 2011-2[676] (Mann 2009[417])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1480)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean 56 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR by 4-variable MDRD formula
Stratum	Overall: GFR <60ml/min/1.73m^2
Subgroup analysis within study	Post-hoc subgroup analysis: GFR <60ml/min/1.73m^2
Inclusion criteria	Age 55 years or older; coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage; intolerant of ACE inhibitors
Exclusion criteria	Patients who needed ARB; hypersensitive or intolerant to ARB; heart failure; significant valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained syncope, planned cardiac surgery, cardiac revascularisation in last 3 months; systolic BP 160mmHg or more; heart transplant; subarachnoid haemorrhage; known significant renal artery stenosis; serum creatinine >3.0mg/dL; hepatic dysfunction; uncorrected volume depletion or sodium depletion; primary aldosteronism; hereditary fructose intolerance; other major non-cardiac illnessreducing life expectancy or interfering with study; use of another experimental drug; disability/incapacity precluding follow up at clinic; no consent
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 69.5 (7.2). Gender (M:F): 670/1480 (45.3%) male . Ethnicity: Asian 20.7%; Arab 1.0%; African 1.0%; European 60.9%; Native or Aboriginal 15.1%; Other 1.2%

Study (subsidiary papers)	Tobe 2011-2[676] (Mann 2009[417])
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: People with cardiovascular disease (Coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage). 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Mean eGFR 50.1 (8.2)
Indirectness of population	No indirectness
Interventions	(n=729) Intervention 1: Angiotensin-II receptor blockers - Telmisartan. Telmisartan 80mg/d. Duration Median 56 months. Concurrent medication/care: Overall (not stated by treatment group): 52.8% statins; 59.9% beta-blockers; 77.5% antiplatelets; 43% diuretics; 41.7% calcium channel blockers (n=751) Intervention 2: Placebo. Placebo. Duration Median 56 months. Concurrent medication/care: Overall (not stated by treatment group): 52.8% statins; 59.9% beta-blockers; 77.5% antiplatelets; 43% diuretics; 41.7% calcium channel blockers
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELMISARTAN versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum
- Actual outcome: Cardiovascular mortality at 56 months; Group 1: 88/729, Group 2: 83/751; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: All-cause mortality at 56 months; Group 1: 133/729, Group 2: 123/751; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome: Chronic dialysis at 56 months; Group 1: 3/729, Group 2: 6/751; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: Dialiysis or doubling of serum creatinine at 5 years; HR 1.29 (95%CI 0.87 to 1.89) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome: Progression from micro- to macro-albuminuria (microalbuminuria subgroup) at 56 months; Group 1: 28/286, Group 2: 49/273; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Tobe 2011-2[676] (Mann 2009[417])
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 124: Tong 2006

Study	Tong 2006[680]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Hong Kong (China); Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Plasma creatinine
Stratum	CKD with diabetes: Type 2 diabetes + moderate renal impairment (plasma creatinine 130-300 micromol/L
Subgroup analysis within study	Not applicable
Inclusion criteria	Type 2 diabetes; age <75; mean plasma creatinine 130-300 micromol/L; treated with oral agents or insulin with stable glycaemic control (HbA1c <10%)
Exclusion criteria	Prior treatmetn with ACEI > 5 years; pregnancy; history of MI; unstable angina or CVA in last 6 months; history of congestive cardiac failure; radiological evidence of obstructive renal disease amenable to surgery or functionally significant renal artery stenosis; microscopic haematuria; urine casts; uncontrolled BP (>200/115mmHg); persistent hyperkalaemia (>5.5mmol/L)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Fosinopril 65.9 (5.5); placebo 65.7 (6.5). Gender (M:F): 15/38 (39%) male. Ethnicity: Chinese
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4.

Study	Tong 2006[680]
	People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline median (IQR) urinary albumin excretion: fosinopril: 1524 (193-4609); placebo 599 (90-3154) - not stated to be signfiicantly different
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: ACE inhibitors - Fosinopril. Fosinopril 10mg daily, increased to 20mg daily at week 4.. Duration 2 years. Concurrent medication/care: 4-week washout of ACEI (if any) before treatment started; from week 4 to week 16, additional antuhypertensive drugs (diuretics, calcium channel blockers, alpha or beta-blockers, centrally acting agents but not ACEI or angiotensin II antagonists) were added or doses increased to meet BP goal of 135/85mmHg. Mean (SD) number of antihypertensive drugs (including test drug): 2 (1). (n=20) Intervention 2: Placebo. Placebo. Duration 2 years. Concurrent medication/care: 4-week washout of ACEI (if any) before treatment started; from week 4 to week 16, additional antuhypertensive drugs (diuretics, calcium channel blockers, alpha or beta-blockers, centrally acting agents but not ACEI or angiotensin II antagonists) were added or doses increased to meet BP goal of 135/85mmHg. Mean (SD) number of antihypertensive drugs (including test drug): 3 (1).
Funding	Study funded by industry (Bristol Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOSINOPRIL versus PLACEBO

Protocol outcome 1: Cardiovascular events (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Cardiovascular mortality, stroke, myocardial infarction, revascularisation, heart failure or unstable angina requiring hospital admission at 2 years; Group 1: 3/18, Group 2: 1/20; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome for CKD with diabetes: Doubling of baseline plasma creatinine or renal replacement therapy at 2 years; Group 1: 4/18, Group 2: 5/20; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Tong 2006[680]
Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Percentage change in urinary albumin excretion at 2 years; Group 1: mean -15.8 % (SD 28); n=18, Group 2: mean 1.1 % (SD 42.5); n=20; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 125: Tutuncu 2001

Study	Tutuncu 2001[687]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in Turkey; Setting: Outpatient clinic
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + microalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	Normotensive; type 2 diabetes; microalbuminuria (UAE 30-300mg/day or 20-200 microg/min in at least 3 consecutive 24-hour samples)
Exclusion criteria	Type 1 diabetes; hypertension (BP >130/85mmHg during ambulatory monitoring and history of antihypertensives); secondary diabetes; thyroid disease; alcoholism; renal insufficiency not related to diabetes; chronic liver disease; overt carcinoma; treated with insulin
Recruitment/selection of patients	Not stated

Study	Tutuncu 2001[687]
Age, gender and ethnicity	Age - Mean (SD): Enalapril: 51.4 (8.0); losartan: 58.1 (10.8); enalapril + losartan: 57.7 (6.2). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline GFR not stated; baseline UAER: enalapril: 85.02 (31.25) mg/d; losartan: 101.66 (41.19) mg/d; enalapril + losartan 102.03 (32.77) mg/d
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: ACE inhibitors - Enalapril. Enalapril 5mg daily. Duration 12 months. Concurrent medication/care: No antihypertensives; no insulin (n=12) Intervention 2: Angiotensin-II receptor blockers - Losartan. Losartan 50mg daily. Duration 12 months. Concurrent medication/care: No antihypertensives; no insulin (n=10) Intervention 3: ACE inhibitors and Angiotensin-II receptor blockers - Enalapril and Losartan. Enalapril 5mg daily + losartan 50mg daily. Duration 12 months. Concurrent medication/care: No antihypertensives; no insulin
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus LOSARTAN

Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum
- Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 12 months; Group 1: mean 35.41 mg/d (SD 19.59); n=12, Group 2: mean 41.33 mg/d (SD 21.08); n=12; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for CKD with diabetes: Regression to normoalbuminuria at 12 months; Group 1: 10/12, Group 2: 8/12; Risk of bias: Unclear; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL AND LOSARTAN versus ENALAPRIL

Study	Tutuncu 2001[687]
	Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 12 months; Group 1: mean 40.7 mg/d (SD 29.52); n=10, Group 2: mean 35.41 mg/d (SD 19.59); n=12; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria at 12 months; Group 1: 7/10, Group 2: 10/12; Risk of bias: Unclear; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL AND LOSARTAN versus LOSARTAN Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 12 months; Group 1: mean 40.7 mg/d (SD 29.52); n=10, Group 2: mean 41.33 mg/d (SD 21.08); n=12; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Regression to normoalbuminuria at 12 months; Group 1: 7/10, Group 2: 8/12; Risk of bias: Unclear; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 126: VA NEPHRON-D

Study	VA NEPHRON-D trial: Fried 2013[214]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1448)
Countries and setting	Conducted in USA; Setting: 32 Department of Veterans Affairs (VA) medical centers
Line of therapy	2nd line

Study	VA NEPHRON-D trial: Fried 2013[214]
Duration of study	Intervention time: Median 2.2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 4-variable MDRD
Stratum	CKD with diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	Veterans with type 2 diabetes, an estimated GFR of 30.0 to 89.9 ml/minute/1.73m^2 and a urinary albumin-to-creatinine ratio of at least 300
Exclusion criteria	Patients with known nondiabetic kidney disease, a serum potassium level of more than 5.5 mmol per liter, current treatment with sodium polystyrene sulfonate, or an inability to stop proscribed medications that increase the risk of hyperkalemia.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Mean 64.7 (7.7) losartan + placebo group and 64.5 (7.9) losartan + lisinopril group. Gender (M:F): 1436:12. Ethnicity: 72.5% White; 23.9% Black; rest "Other"
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Indirectness of population	No indirectness
Interventions	(n=724) Intervention 1: ACE inhibitors and Angiotensin-II receptor blockers - Lisinopril and Losartan. Losartan 50-100mg/day + lisinopril 10-40mg/day. Duration Median 2.2 years. Concurrent medication/care: Diuretic 71.3%; Calcium-channel blocker 59.3%; Beta-blocker 69.9%; Alpha-blocker 21.0%; other blood-pressure medications at randomization: 20.3% (n=724) Intervention 2: Angiotensin-II receptor blockers - Losartan. Losartan 50-100mg/day. Duration Median 2.2 years. Concurrent medication/care: Diuretic 70.3%; Calcium-channel blocker 57.1%; Beta-blocker 68.7%; Alpha-blocker 21.9%; other blood-pressure medications at randomization: 20.3%
Funding	Equipment / drugs provided by industry (Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; Investigator-Initiated Studies Program of Merck provided the study drugs)

Study	VA NEPHRON-D trial: Fried 2013[214]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL AND LOSARTAN versus LOSARTAN Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Mortality at Median 2.2 years; Group 1: 63/724, Group 2: 60/724; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular events (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: MI, heart failure or stroke at Median 2.2 years; Group 1: 134/724, Group 2: 136/724; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: ESRD at Median 2.2 years; Group 1: 27/724, Group 2: 43/724; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Acute kidney injury (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Acute kidney injury at Median 2.2 years; Group 1: 130/724, Group 2: 80/724; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 127: Van den meiracker 2006

Study	Van den meiracker 2006[692]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=59)
Countries and setting	Conducted in Netherlands; Setting: Outpatient clinic

Study	Van den meiracker 2006[692]
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urinary albumin excretion
Stratum	CKD with diabetes: Type 2 diabetes + macroalbuminuria
Subgroup analysis within study	Not applicable
Inclusion criteria	type 2 diabetes; 24 hour urinary albumin excretion >300mg or urinary albumin:creatinine ratio >20mg/mmol despite use of ACEI or ARB in recommended doses for at least 1 year; retinopathy; age 20-80 years
Exclusion criteria	Clinical or laboratory evidence of other kidney or renal tract disease; serum creatinine >265micromol/L; serum potassium >5mmol/L; underlying malignant, hepatic or gastrointestinal disease; MI or stroke in last 3 months; unstable angina; alcohol or drug abuse; psychological illness
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: Geometric mean (IQR): spironolactone 55.2 (38-78); placebo 55.2 (29-75). Gender (M:F): 39/59 (66%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Geometric mean (IQR) eGFR (MDRD formula): spironolactone 87 (67-109); placebo 64 (47-87); p=0.02 for difference
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Aldosterone antagonists - Spironolactone. Spironolactone 50mg once daily in the morning; reduced to 25mg if serum potassium increased to >5.5mmol/L after 2 weeks; if still >5.5mmol/L after 2 weeks on lower dose, patient withdrawn. Duration 1 year. Concurrent medication/care: Continued previous antihypertensive drugs: 17 ACEI (mostly enalapril, mean dose 25mg, range 20-60mg); 7 ARB (mostly losartan 100mg; remainder candesartan 16mg or valsartan 160mg); 13 non-potassium sparing diuretic; 9 calcium channel blocker; 9 beta-blocker; 3 alpha blocker; mean number of antihypertensives 2.2 (n=30) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Continued previous antihypertensive drugs: 25 ACEI (mostly enalapril, mean dose 25mg, range 20-60mg); 4 ARB (mostly losartan 100mg;

Study	Van den meiracker 2006[692]
	remainder candesartan 16mg or valsartan 160mg); 13 non-potassium sparing diuretic; 13 calcium channel blocker; 9 beta-blocker; 1 alpha blocker; mean number of antihypertensives 2.3
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SPIRONOLACTONE versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: All-cause mortality at 1 year; Group 1: 0/24, Group 2: 2/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD with diabetes: Change in eGFR at 1 year; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Urinary albumin:creatinine ratio at 1 year; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 128: Viberti 1994

Study	Viberti 1994[701]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=92)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient clinics
Line of therapy	1st line

Study	Viberti 1994[701]
Duration of study	Intervention time: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Albumin excretion rate
Stratum	CKD with diabetes: Type 1 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	Insulin dependent diabetes mellitus diagnosed before age 39; age 18-55 years; duration of diabetes 4-28 years; AER 20-200 microg/min in at least 2 of 3 consecutive overnight samples; BP <160/95mmHg if age 35 or older or <145/90mmHg if <35 years; no antihypertensive drugs
Exclusion criteria	On or previously treated with antihypertensive drugs, NSAIDs or aldose-reductase inhibitors; brittle diabetes; insulin resistance (needing >120U/day); history of poor compliance; serum creatinine >1.7mg/dL; raised serum potassium; other renal, endocrine, cardiac, liver, gastrointestinal or connective tissue diseases
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): Captopril 32 (19-54); placebo 31 (18-52). Gender (M:F): 51/92 (55%) male. Ethnicity: 87/92 European; 5 Oriental
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline mean (95% CI) measured GFR: captopril 124 (116-132) ml/min/1.73m^2; placebo 136 (127-145), p<0.04 for difference
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: ACE inhibitors - Captopril. Captopril 50mg twice daily. Duration 24 months. Concurrent medication/care: Usual insulin and diet; no antihypertensives (n=46) Intervention 2: Placebo. Placebo. Duration 24 months. Concurrent medication/care: Usual insulin and diet; no antihypertensives
Funding	Study funded by industry (Bristol-Myers Squibb)

Study	Viberti 1994[701]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD with diabetes: Progression to macroalbuminuria at 24 months; Group 1: 4/44, Group 2: 12/44; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD with diabetes: Urinary albumin excretion rate at 24 months; Group 1: mean 2.1 % per year (SD 13.4); n=44, Group 2: mean 18.3 % per year (SD 19.7); n=44; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum; Progression of CKD (change in eGFR) (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

Table 129: Woo 2009

Study	Woo 2009[724]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=226)
Countries and setting	Conducted in Singapore; Setting: Outpatient clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Biopsy-proven IgA nephritis
Stratum	CKD without diabetes: IgA nephritis
Subgroup analysis within study	Not applicable
Inclusion criteria	Biopsy-proven IgA nephritis; proteinuria 1g or more; CKD stage 3

Study	Woo 2009[724]
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): High dose losartan: 34 (10); normal dose losartan 32 (12); normal dose enalapril 32 (10); low dose enalapril 34 (11). Gender (M:F): 110/207 completers (53%) male. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: 2. Older people aged 75 or over: 3. People with cardiovascular disease: 4. People with diabetes and proteinuria: 5. People with hypertension: 6. People with proteinuria :
Extra comments	Baseline eGFR: High dose losartan: 63.5 (24.2); normal dose losartan 61.2 (18.4); normal dose enalapril 62.0 (20.8); low dose enalapril 60.9 (19.8) ml/min
Indirectness of population	No indirectness
Interventions	(n=112) Intervention 1: Angiotensin-II receptor blockers - Losartan. Losartan high dose 200mg or normal dose 100mg. Duration 6 years. Concurrent medication/care: Additional BP control with atenolol, amlodipine and nifedipine with target BP < 130/80mmHg Comments: High dose losartan: 67 patients; normal dose losartan 45 patients (n=114) Intervention 2: ACE inhibitors - Enalapril. Enalapril normal dose 20mg or low dose 10mg. Duration 6 years. Concurrent medication/care: Additional BP control with atenolol, amlodipine and nifedipine with target BP < 130/80mmHg Comments: Normal dose enalapril 69 patients; low dose enalapril 45 patients
Funding	Other (Hospital Division of Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus ENALAPRIL

Protocol outcome 1: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 12 months minimum
- Actual outcome for CKD without diabetes: ESRD (losartan high dose vs. enalapril normal dose) at 6 years; Group 1: 7/63, Group 2: 19/61; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for CKD without diabetes: ESRD (losartan high dose vs. enalapril low dose) at 6 years; Group 1: 7/63, Group 2: 9/40; Risk of bias: Unclear; Indirectness

Study	Woo 2009[724]
of outcome: No indirectness - Actual outcome for CKD without diabetes: ESRD (losartan normal dose vs. enalapril normal dose) at 6 years; Group 1: 9/43, Group 2: 19/61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: ESRD (losartan normal dose vs. enalapril low dose) at 6 years; Group 1: 9/43, Group 2: 9/40; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (change in eGFR) (Critical) at 12 months minimum - Actual outcome for CKD without diabetes: eGFR (losartan high dose vs. enalapril normal dose) at 6 years; Group 1: mean 59.1 ml/min (SD 31.8); n=63, Group 2: mean 41.3 ml/min (SD 27.9); n=61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: eGFR (losartan high dose vs. enalapril low dose) at 6 years; Group 1: mean 59.1 ml/min (SD 31.8); n=63, Group 2: mean 42.3 ml/min (SD 26.6); n=40; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: eGFR (losartan normal dose vs. enalapril normal dose) at 6 years; Group 1: mean 40.2 ml/min (SD 27.6); n=43, Group 2: mean 41.3 ml/min (SD 27.9); n=61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: eGFR (losartan normal dose vs. enalapril low dose) at 6 years; Group 1: mean 40.2 ml/min (SD 27.6); n=43, Group 2: mean 42.3 ml/min (SD 26.6); n=40; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Change in proteinuria (ACR, PCR or 24 hour urinary protein) (Important) at 12 months minimum - Actual outcome for CKD without diabetes: Urinary protein g/day (losartan high dose vs. enalapril normal dose) at 6 years; Group 1: mean 1.2 g/day (SD 0.8); n=63, Group 2: mean 1.7 g/day (SD 1); n=61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Urinary protein g/day (losartan high dose vs. enalapril low dose) at 6 years; Group 1: mean 1.2 g/day (SD 0.8); n=63, Group 2: mean 1.7 g/day (SD 0.9); n=40; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Urinary protein g/day (losartan normal dose vs. enalapril normal dose) at 6 years; Group 1: mean 1.6 g/day (SD 0.9); n=43, Group 2: mean 1.7 g/day (SD 1); n=61; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for CKD without diabetes: Urinary protein g/day (losartan normal dose vs. enalapril low dose) at 6 years; Group 1: mean 1.6 g/day (SD 0.9); n=43, Group 2: mean 1.7 g/day (SD 0.9); n=40; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 12 months minimum; Cardiovascular events (Critical) at 12 months minimum; Hospitalisation (Important) at 12 months minimum; Acute kidney injury (Critical) at 12 months minimum; Health related quality of life (Important) at 12 months minimum

G.10 Oral antiplatelets and anticoagulants

Table 130: Agnelli 2013

Study	Agnelli 2013[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2486 enrolled)
Countries and setting	Conducted in Multiple countries; Setting: Not stated (hospitals)
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 year intended treatment period and 30 days follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Mild or moderate renal impairment. Assessment method not stated.
Stratum	Overall:
Subgroup analysis within study	Not stratified but pre-specified: Renal impairment subgroup
Inclusion criteria	18 years or older; objectively confirmed symptomatic deep-vein thrombosis or pulmonary embolism; treated for 6 to 12 months with standard anticoagulant therapy or had completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial; no sympatomatic recurrence during prior anticoagulant therapy; clinical equipoise about the continuation or cessation of anticoagulant therapy.
Exclusion criteria	Contraindication to continued anticoagulant therapy or if they required ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose higher than 165mg daily. Haemoglobin level of less than 9mg per decileter, platelet count of less than 100,00 per cubic mm, serum creatinine >2.5mg/deciliter or creatinine clearance of <25ml/min, alanine amino-transferase or aspartate aminotransferase level >2 times the upper limit of normal range, or total bilirubin level >1.5 times the normal range.
Recruitment/selection of patients	Randomisation with an interactive voice-response system stratified according to initial diagnosis (deep-vein thrombosis or pulmonary embolism) and participation or no participation in the AMPLIFY trial.

Study	Agnelli 2013[18]
Age, gender and ethnicity	Age - Mean (SD): Apixaban 2.5mg: 56.6 (15.3), Apixaban 5mg: 56.4 (15.6), Placebo 57.1 (15.2). NB overall group only - not CKD subgroup.. Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Older people aged 75 or over: Not applicable / Not stated / Unclear (Age range not stated. Average age only 56-57.). 2. People with cardiovascular disease: People with cardiovascular disease (All participants had pulmonary embolism and/or deep vein thrombosis.).
Extra comments	Particiapnts were enrolled within approximately 7 days after they received the last dose of prior anticoagulant therapy and, if they were receiving a vitamin K antagonist, when the INR was 2.0 or lower.
Indirectness of population	Serious indirectness: All participants had either pulmonary embolism and/or deep vein thrombosis.
Interventions	(n=842) Intervention 1: Oral anticoagulants - Apixaban. Apixiban 2.5mg. Duration 1 year. Concurrent medication/care: Drugs prohibited during the course of the trial: dual antiplatelet therapy, aspirin >165mg daily and potent inhibitors of cytochrome P-450 3A4 and P-glycoprotein. Comments: 2 participants excluded because verifiable source documentation was lacking. (n=815) Intervention 2: Oral anticoagulants - Apixaban. Apixaban 5mg. Duration 1 year. Concurrent medication/care: Drugs prohibited during the course of the trial: dual antiplatelet therapy, aspirin >165mg daily and potent inhibitors of cytochrome P-450 3A4 and P-glycoprotein. Comments: 2 participants excluded because verifiable source documentation was lacking. (n=829) Intervention 3: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Drugs prohibited during the course of the trial: dual antiplatelet therapy, aspirin >165mg daily and potent inhibitors of cytochrome P-450 3A4 and P-glycoprotein.
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN 2.5MG versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum	

Study	Agnelli 2013[18]
- Actual outcome: Composite of all-cause mortality or symptomatic recurrent venous thromboembolism. Severe or moderate renal impairment. at 1 year; Group 1: 5/48, Group 2: 7/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of all-cause mortality or symptomatic recurrent venous thromboembolism. Mild renal impairment. at 1 year; Group 1: 7/174, Group 2: 26/194; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Composite of symptomatic recurrent venous thromboembolism or death related to venous thromboembolism. Severe or moderate renal impairment. at 1 year; Group 1: 2/48, Group 2: 5/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of symptomatic recurrent venous thromboembolism or death related to venous thromboembolism. Mild renal impairment. at 1 year; Group 1: 5/174, Group 2: 23/194; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Composite of major and clinically relevant non-major bleeding. Severe or moderate renal impairment. at 1 year; Group 1: 4/48, Group 2: 2/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of major and clinically relevant non-major bleeding. Mild renal impairment. at 1 year; Group 1: 7/174, Group 2: 3/193; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN 5MG versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum - Actual outcome: Composite of all-cause mortality or symptomatic recurrent venous thromboembolism. Severe or moderate renal impairment. at 1 year; Group 1: 1/44, Group 2: 7/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of all-cause mortality or symptomatic recurrent venous thromboembolism. Mild renal impairment. at 1 year; Group 1: 7/168, Group 2: 26/194; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Composite of symptomatic recurrent venous thromboembolism or death related to venous thromboembolism. Severe or moderate renal impairment. at 1 year; Group 1: 0/44, Group 2: 5/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of symptomatic recurrent venous thromboembolism or death related to venous thromboembolism. Mild renal impairment. at 1 year;	

Study	Agnelli 2013[18]
Group 1: 5/168, Group 2: 23/194; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Composite of major and clinically relevant non-major bleeding. Severe or moderate renal impairment. at 1 year; Group 1: 6/43, Group 2: 2/46; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness - Actual outcome: Composite of major and clinically relevant non-major bleeding. Mild renal impairment. at 1 year; Group 1: 7/168, Group 2: 3/193; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

Table 131: Alexander 2011

Study	Alexander 2011[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=7392)
Countries and setting	Conducted in Multiple countries; Setting: 858 sites in 39 countries
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 241 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not stated
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Level of renal impairment (severe or moderate, mild, or normal renal function)
Inclusion criteria	ACS (MI +/-ST-elevation or unstable angina) in previous 7 days, with symptoms of myocardial ischemia lasting 10 mins

Study	Alexander 2011[28]
	or more with patient at rest + elevated cardiac biomarkers or dynamic ST-segment depression or elevation of 0.1 mV or more; clinically stable and on standard treatment including aspirin or aspirin plus any P2Y12-receptor antagonist; + 2 or more high risk characteristics (age at least 65 years; diabetes; MI in last 5 years; cerebrovascular or peripheral vascular disease; heart failure or LVEF <40% with index event; imparied renal function with creatinine clearance <60ml/min; no revascularisation after index event)
Exclusion criteria	persistent severe hypertension, severe renal dysfunction with calculated creatinine clearance <20ml/min; active bleeding or a high risk for bleeding; known coagulopathy; ischemic stroke within 7 days; NYHA class IV; any history of intracranial bleeding; hemoglobin <9g/dL; platelet count <100,000mm3; required ongoing treatment with a parenteral or oral anticoagulant; required treatment with highdose aspirin (>325 mg daily) or a strong inhibitor of CYP3A4; a severe comorbid condition with life expectancy of ≤6 months; acute pericarditis, active hepatobiliary disease, and women who were pregnant, breastfeeding, or of childbearing potential and unable to use an acceptable method of birth control
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (range): 67 (IQR 58-74). Gender (M:F): 5014:2378. Ethnicity: White 5583; Black/African American 173; Asian 1318; Other 318
Further population details	1. Older people aged 75 or over: Mixed 2. People with cardiovascular disease: People with cardiovascular disease (Whole sample ACS; subgroup with renal disease).
Indirectness of population	Serious indirectness: Patients with recent ACS and ≥2 risk factors for recurrent ischaemic events
Interventions	(n=3705) Intervention 1: Oral anticoagulants - Apixaban. Apixaban 5mg twice daily. Duration Median 240 days. Concurrent medication/care: ACE inhibitor 2434/3705 (65.7%); ARB 527 (14.2%); Beta-blocker 2853 (77.0%); Statin 3076 (83.0%); Proton-pump inhibitor 894 (24.1%) (n=3687) Intervention 2: Placebo. Placebo. Duration Median 242 days. Concurrent medication/care: ACE inhibitor 2406/3687 (65.3%); ARB 503 (13.6%); Beta-blocker 2816 (76.4%); Statin 3105 (84.2%); Proton-pump inhibitor 906 (24.6%)
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer)

Study	Alexander 2011[28]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus PLACEBO Protocol outcome 1: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: CV death, MI or ischaemic stroke (moderate/severe renal impairment) at 241 days; HR 0.94 (95%CI 0.69 to 1.29); Risk of bias: Low; Indirectness of outcome: Serious indirectness - Actual outcome: CV death, MI or ischaemic stroke (mild renal impairment) at 241 days; Mean 1.04 (95%CI 0.79 to 1.36); Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: TIMI major bleeding (moderate/severe renal impairment) at Median 241 days; Mean 4.94 (95%CI 1.42 to 17.22); Risk of bias: Low; Indirectness of outcome: Serious indirectness - Actual outcome: TIMI major bleeding (mild renal impairment) at Median 241 days; Mean 1.3 (95%CI 0.57 to 2.96); Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

Table 132: Best 2008

Study	Best 2008[68]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=331)
Countries and setting	Conducted in Canada, USA; Setting: Hospitals

Study	Best 2008[68]
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum creatinine level; creatinine clearance calcuated using Cockcroft-Gault formula
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Elective PCI planned or considered likely (symptomatic coronary artery disease; objective evicdence of ischaemia; at least 21 years old; provided consent and agreed to protocol specified procedures)
Exclusion criteria	Serum creatinine not available at study entry; contraindications to antiplatelet/anticoagulant therapy; >50% stenosis of left main coronary artery; failed coronary intervention in last 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomisation; planned staged interventional procedure; GpIIb-IIIa inhibitor within 7 days; clopidogrel within 10 days; thrombolytics within 24 hours.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 73.5 (8.1). Gender (M:F): 54.4% male. Ethnicity: Not stated
Further population details	1. Older people aged 75 or over: Mixed (Mean 73.5 (8.1) years). 2. People with cardiovascular disease: People with cardiovascular disease (All symptomatic coronary artery disease).
Extra comments	Diabetes: 26.55%, hypertension: 72.35, previous CABG: 25.3%, previous PCI: 35.3%, previous MI: 35.45%, peripheral vascular disease: 12,9%, CHF: 12.7%.. Creatinine clearance <60ml/min. All previous cardiac events or interventions slightly higher in group with eGFR<60.
Indirectness of population	Serious indirectness: All participants had a planned elective PCI of single or multiple vessels
Interventions	(n=166) Intervention 1: Antiplatelet agents - Clopidogrel. 300mg 3-24 hours before PCI; after procedure, 75mg daily for 1 year. Duration 1 year. Concurrent medication/care: Aspirin 325mg daily for 28 days then 81-325mg daily for 1 year Comments: Number randomised not stated: 166 is around half of the 331 total (n=165) Intervention 2: Placebo. placebo. Duration 1 year. Concurrent medication/care: Aspirin 325mg daily for 28

Study	Best 2008[68]
	days then 81-325mg daily for 1 year Comments: Number randomsied not stated: 165 is around half of the total of 331
Funding	Study funded by industry (Bristol-Meyers Squibb/Sanofi-Synthelabo partnership)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus PLACEBO Protocol outcome 1: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Death, MI or stroke CrCl < 60ml/min at 1 year; HR 1.41 (95%CI 0.81 to 2.45) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Death, MI or stroke CrCl 60-89 ml/min at 1 year; HR 0.8 (95%CI 0.51 to 1.25) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Major bleeding CrCl <60ml/min at 1 year; Mean 1.124 (95%CI 0.511 to 2.476); Risk of bias: Unclear; Indirectness of outcome: - Actual outcome: Major bleeding CrCl 60-89ml/min at 1 year; Mean 1.595 (95%CI 0.97 to 2.621); Risk of bias: Unclear; Indirectness of outcome: - Actual outcome: Minor bleeding CrCl <60ml/min at 1 year; Mean 0.546 (95%CI 0.25 to 1.189); Risk of bias: Unclear; Indirectness of outcome: Protocol outcome 3: Minor bleeding (as reported by the studies) (Important) at Define - Actual outcome: Minor bleeding CrCl 60-89 ml/min at 1 year; RR 1.579 (95%CI 0.883 to 2.825); Risk of bias: Unclear; Indirectness of outcome:	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 133: Dasgupta 2009

Study	Dasgupta 2009[150]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2009)
Countries and setting	Conducted in Multiple countries; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention time: Median 28 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diabetic nephropathy (diabetes plus microalbuminuria; albumin 30 microg/ml or more)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinically evident cardiovascular disease or multiple atherothrombotic risk factors for cardiovascular disease.
Exclusion criteria	No active acute coronary syndrome at enrolment.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 63.1 years. Gender (M:F): 33% female. Ethnicity: 68.8% White; 14.7% Hispanic; 9.1% Asian; 4.2% Black; 3.2% Other
Further population details	1. Older people aged 75 or over: Not applicable / Not stated / Unclear (Mean 63 years; SD or range not stated). 2. People with cardiovascular disease: People with cardiovascular disease (Clinically evident cardiovascular disease or multiple atherothrombotic risk factors for CV disease).
Extra comments	. Hypertension: 86.2% placebo, 88.7% clopidogrel. CHF: 6.8% placebo, 7.6% clopidogrel. Previous MI: 19.6% placebo, 18.2% clopidogrel, AF: 3.1% placebo, 3.3% clopidogrel. Previous stroke: 8.7% placebo, 8.2% clopidogrel. Previous TIA: 4.3% placebo, 3.8% clopidogrel. Peripheral arterial disease: 16.2% placebo, 14.7% clopidogrel. Previous PCI: 11.3% placebo, 10.1% clopidogrel. Previous CABG: 15.3% placebo, 13.1% clopidogrel. Previous carotid endocardectomy: 2.9% placebo, 2.7% clopidogrel. Previous peripheral angioplasty: 6.6% placebo, 5.4% clopidogrel.
Indirectness of population	Serious indirectness: People with clinically evidence cardiovascular disease (symptomatic patients) or multiple

Study	Dasgupta 2009[150]
	atherothrombotic risk factors for cardiovascular disease. Subgroup analysis of those with diabetic nephropathy.
Interventions	(n=1006) Intervention 1: Antiplatelet agents - Clopidogrel. 75mg daily. Duration Median 28 months. Concurrent medication/care: 75-162mg aspirin daily (n=1003) Intervention 2: Placebo. Placebo. Duration Median 28 months. Concurrent medication/care: 75-162mg aspirin daily
Funding	Study funded by industry (Bristol-Myers Squibb, Sanofi Aventis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum
- Actual outcome: All-cause mortality at Median 28 months; HR 1.6 (95%CI 1.1 to 2.4) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: Cardiovascular mortality at Median 28 months; HR 1.7 (95%CI 1.1 to 2.6) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum
- Actual outcome: Non-fatal myocardial infarction at Median 28 months; HR 0.8 (95%CI 0.4 to 1.3) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: Non-fatal stroke at Median 28 months; HR 0.9 (95%CI 0.5 to 1.7) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: Hospitalisation (Important) at 6 months minimum
- Actual outcome: Hospitalisation at Median 28 months; HR 0.9 (95%CI 0.7 to 1.2) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Major bleeding (as reported by studies) (Critical) at 6 months minimum
- Actual outcome: GUSTO severe bleeding at Median 28 months; HR 1.8 (95%CI 0.9 to 3.3) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Minor bleeding (as reported by the studies) (Important) at Define
- Actual outcome: GUSTO moderate bleeding at Median 28 months; HR 1.2 (95%CI 0.7 to 2) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Dasgupta 2009[150]
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 134: Eikelboom 2012

Study	Eikelboom 2012[180]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=5525 totoal, 3828 eGFR≥60, 1697 eGFR,60ml/min/1.73m^2)
Countries and setting	Conducted in Multiple countries; Setting: 522 clinical sites.
Line of therapy	Adjunctive to current care
Duration of study	Not clear: Mean follow-up 1.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cockroft-Gault.
Stratum	Overall: Cardiovascular disease (all participants had atrial fibrillation)
Subgroup analysis within study	Unclear: People with stage III CKD
Inclusion criteria	Permanent or paroxysmal atrial fibrillation if they had ≥1 of the following additional risk factors for stroke: previous stroke or transient ischemic attack; age ≥75 years, arterial hypertension on treatment; diabetes mellitus; heart failure, left ventricular ejection fraction <35%; or documented peripheral arterial disease.
Exclusion criteria	Candidates for oral anticoagulation with a vitamin K antagonist either because anticoagulant therapy had been demonstrated or was expected to be unsuitable.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (SD): 75. Gender (M:F): 51% male. Ethnicity: 59% white (other ethnicities not stated)
Further population details	1. Older people aged 75 or over: Mixed 2. People with cardiovascular disease: People with cardiovascular disease (All

Study	Eikelboom 2012[180]
	participants had atrial fibrillation.).
Extra comments	For Stage III CKD (eGFR<60 ml/min/1.73m^2) 88% had hypertension, 22% had diabetes, 43% had heart failure, 16% previous stroke / TIA. Mean daily aspirin dose: 120mg. Mean eGFR: 49ml/min/1.73m^2.
Indirectness of population	Serious indirectness: All participants had atrial fibrillation.
Interventions	(n=857) Intervention 1: Oral anticoagulants - Apixaban. Apixaban 5mg twice daily (reduced dose of 2.5mg twice daily was assigned to participants who met 2 of the following criteria: (1) age≥80 years, (2) body weight <60kg, or (3) serum creatinine ≥1.5mg/dL or 133 micromol/L).. Duration Mean 1.1 years. Concurrent medication/care: Not stated. (n=840) Intervention 2: Antiplatelet agents - Aspirin. 81 to 324 mg daily. Duration Mean 1.1 years.. Concurrent medication/care: Not stated.
Funding	Study funded by industry (Bristol-Myers-Squibb and Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus ASPIRIN Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum - Actual outcome: All-cause mortality at Mean 1.1 years; HR 0.86 (95%CI 0.61 to 1.2) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Stroke or systemic embolism at Mean 1.1 years; HR 0.32 (95%CI 0.18 to 0.55) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Major haemorrhage at Mean 1.1 years; HR 1.2 (95%CI 0.65 to 2.1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life

Study	Eikelboom 2012[180]
	(Important) at 6 months minimum

Table 135: Fox 2011

Study	Fox 2011[209]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=14264)
Countries and setting	Conducted in Multiple countries; Setting: Hospitals in 45 countries.
Line of therapy	1st line
Duration of study	Follow up (post intervention): Median 1.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cockcroft-Gault method Cr Cl 30-49ml/min
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ECG documented non-valvular atrial fibrillation and at moderate to high risk of stroke (history of stroke, TIA or systemic embolism or at least two of heart failure, LVEF 35% or less, hypertension, age 75 or more, diabetes).
Exclusion criteria	High risk of bleeding (including prior intracerebral bleeding, surgical trauma within 30 days, gastrointestinal bleeding within 6 months). People with a creatinine clearance <30ml/min.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): 79 (75, 83). Gender (M:F): 1314/1636. Ethnicity: Not stated
Further population details	1. Older people aged 75 or over: Mixed (Median age 79, 25th percentile 75). 2. People with cardiovascular disease: People with cardiovascular disease (All had atrial fibrillation.).
Extra comments	36% were taking aspirin. Prior TIA/stroke or systemic embolism: 52.85%, CHF: 63.65, hypertension: 91%, diabetes: 37.2%, prior MI: 18.13, peripheral vascular disease: 6.5%.
Indirectness of population	Serious indirectness: All participants had non-valvular atrial fibrilation and moderate to high risk of stroke. (Subgroup

Study	Fox 2011[209]
	ananlysis of those with moderate renal impairment (creatinine clearance 30-49ml/min).
Interventions	(n=1474) Intervention 1: Oral anticoagulants - Rivaroxaban. 15mg daily. Duration Not stated. Concurrent medication/care: Not stated (n=1476) Intervention 2: Oral anticoagulants - Warfarin. Dose adjusted to target INR 2.0 to 3.0. Duration Not stated. Concurrent medication/care: Not stated
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus WARFARIN Protocol outcome 1: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Ischaemic stroke at Not stated; HR 1.11 (95%CI 0.71 to 1.73) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Haemorrhagic stroke at Not stated; HR 0.56 (95%CI 0.21 to 1.51) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Undetermined stroke at Not stated; HR 0.51 (95%CI 0.05 to 5.67) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Major bleeding (including haemoglobin drop, transfusion, clinical organ and fatal bleeding) at Not stated; HR 0.95 (95%CI 0.72 to 1.26) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Intracranial haemorrhage at Not stated; HR 0.81 (95%CI 0.41 to 1.6) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

Table 136: HJAZI 2014

Study	RE-LY trial: Hijazi 2014[266]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=17951)
Countries and setting	Conducted in Unknown multicentre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Assumed receiving study drug throughout follow-up period.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CKD-EPI, Cockroft Gault and MDRD equations all used. Results reported here are for CKD-EPI.
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Pre-specified subgroup analysis by renal function
Inclusion criteria	People with atrial fibrillation (AF) and at least one of the following characteristics: previous stroke or transient ischaemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II of higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.
Exclusion criteria	Presence of a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of haemorrhage, a creatinine clearance of less than 30 ml/min, acute liver disease, and pregnancy.
Recruitment/selection of patients	Randomised 1:1:1.
Age, gender and ethnicity	Age - Mean (SD): >80ml/min: 66.9 (9.7), 50-80ml/min: 72 (8), <50ml/min: 75.2 (7.2).. Gender (M:F): >80ml/min: 70.5% M, 50-80ml/min: 64.3% M, <50ml/min: 53.4% M.. Ethnicity: Not reported.
Further population details	1. Older people aged 75 or over: Systematic review: mixed (Range 22-101 years.). 2. People with cardiovascular disease: People with cardiovascular disease (AF and at least 1 other risk factor for stroke.).
Extra comments	Dose of dabigatran blinded, warfarin was unblinded (except for study administrators).
Indirectness of population	No indirectness

Study	RE-LY trial: Hijazi 2014[266]
Interventions	(n=5957) Intervention 1: Oral anticoagulants - Dabigatran. 110mg BID. Duration Median 2 years. Concurrent medication/care: Not stated. (n=6029) Intervention 2: Oral anticoagulants - Dabigatran. 150 mg BID. Duration Median 2 years. Concurrent medication/care: Not stated. (n=5965) Intervention 3: Oral anticoagulants - Warfarin. Adjusted dose, target INR 2-3.. Duration Median 2 years. Concurrent medication/care: Not stated.
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN 110mg versus WARFARIN

Protocol outcome 1: Mortality (all cause and cardiovascular) (Critical) at 6 months minimum
- Actual outcome: All-cause mortality - >80ml/min at 2 years; HR 0.82 (95%CI 0.6 to 1.12) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness
- Actual outcome: All-cause mortality - 50-80ml/min at 2 years; HR 0.88 (95%CI 0.74 to 1.05) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness
- Actual outcome: All-cause mortality - 30-50ml/min at 2 years; HR 0.97 (95%CI 0.77 to 1.24) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum
- Actual outcome: Stroke or systemic embolism - >80ml/min at 2 years; HR 0.87 (95%CI 0.53 to 1.45) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness
- Actual outcome: Stroke or systemic embolism - 50-80ml/min at 2 years; HR 0.94 (95%CI 0.73 to 1.21) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness

Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum
- Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - >80ml/min at 2 years; HR 0.41 (95%CI 0.27 to 0.62) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness
- Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - 50-80ml/min at 2 years; HR

Study	RE-LY trial: Hijazi 2014[266]
0.82 (95%CI 0.68 to 0.99) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - 30-50ml/min at 2 years; HR 1.02 (95%CI 0.78 to 1.33) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN 150mg versus WARFARIN Protocol outcome 1: Mortality (all cause and cardiovascular) (Critical) at 6 months minimum - Actual outcome: All-cause mortality - >80ml/min at 2 years; HR 0.7 (95%CI 0.5 to 0.97) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: All-cause mortality - 50-80ml/min at 2 years; HR 0.85 (95%CI 0.71 to 1.02) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: All-cause mortality - 30-50ml/min at 2 years; HR 1.03 (95%CI 0.82 to 1.3) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Stroke or systemic embolism - 30-50ml/min at 2 years; HR 0.78 (95%CI 0.51 to 1.21) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Stroke or systemic embolism - >80ml/min at 2 years; HR 0.65 (95%CI 0.37 to 1.12) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Stroke or systemic embolism - 50-80ml/min at 2 years; HR 0.69 (95%CI 0.52 to 0.9) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Stroke or systemic embolism - 30-50ml/min at 2 years; HR 0.55 (95%CI 0.34 to 0.89) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - >80ml/min at 2 years; HR 0.59 (95%CI 0.41 to 0.84) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - 50-80ml/min at 2 years; HR 0.9 (95%CI 0.75 to 1.09) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness - Actual outcome: Reduction in harmoglobinlevel >20g/L, transfusion of > 2U of blood, or symptomatic bleeding in a cretical area or organ - 30-50ml/min at 2 years; HR 1.22 (95%CI 0.95 to 1.58) Reported; Risk of bias: --; Indirectness of outcome: Serious indirectness	

Study	RE-LY trial: Hijazi 2014[266]
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum.

Table 137: Hohnloser 2012

Study	Hohnloser 2012[275]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=eGFR >50-80ml/min: 5272, eGFR ≤50ml/min: 2067)
Countries and setting	Conducted in Multiple countries; Setting: Multicentre
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 1.8 years.Uncle
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessed by Cockcroft Gault, CKD-EPI or Cystatin C (results of each reported).
Stratum	Overall: All participants had atrial fibrillation.
Subgroup analysis within study	Post-hoc subgroup analysis: CKD
Inclusion criteria	Atrial fibrillation or flutter at enrolment or at least two episodes documented by electrocardiography at least 2 weeks apart in the 12 months before enrolment. In addition, at least one of the following risk factors for stroke was required: age greater or equal to 75 years; prior stroke, TIA or systemic embolism, symptomatic heart failure within 3 months or left ventricular ejection fraction of no more than 40%, diabetes mellitus, hypertension requiring pharmacological treatment.
Exclusion criteria	Atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation such as prosthetic heart valve, stroke within 7 days, need for aspirin >165mg a day or

Study	Hohnloser 2012[275]
	both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine >2.5mg/dL or calculated creatinine clearance <25ml/min.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (SD): eGFR 50-80 ml/min: 70.3 (9.1), eGFR ≤50ml/min: 73.3 (8.7). Gender (M:F): eGFR 50-80 ml/min: 36% female, eGFR ≤50ml/min: 38% female. Ethnicity: Unclear - assumed mixed (study sites were in North America, Latin America, Europe and Asian Pacific regions).
Further population details	1. Older people aged 75 or over: Mixed 2. People with cardiovascular disease: People with cardiovascular disease (All participants had atrial fibrillation.).
Extra comments	For eGFR≤50ml/min: BP: 129.7/76.9, Prior myocardial infarction 18.5%, congestive heart failure 41.8%, prior stroke, TIA or systemic embolism 23%, diabetes 29.8%, hypertension 89.6%, prior clinically relevant or spontaneous bleeding 20.5%. 10.9% paroxysmal atrial fibrillation, 89.1% persistent or permanent.
Indirectness of population	Serious indirectness: All participants had atrial fibrillation.
Interventions	(n=1422) Intervention 1: Oral anticoagulants - Apixaban. 5mg twice daily or 2.5mg twice daily for people with two or more of the following: aged 80 or over, weight 60kg or under, serum creatinine 1.5mg/dL or more.. Duration Median 1.8 years. Concurrent medication/care: Not stated. Comments: Number not given per intervention - assumed 50/50 from total n with eGFR <50 from CKD-EPI 2843 ((n=1422) Intervention 2: Oral anticoagulants - Warfarin. 2mg tablets adjusted to achieve a target INR of 2-3.. Duration Median 1.8 years. Concurrent medication/care: Not stated Comments: Number not given per intervention - assumed 50/50 from total n with eGFR <50 from CKD-EPI 2843
Funding	Study funded by industry (Bristol-Myers Squibb and Pfizer.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: APIXABAN versus WARFARIN

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum
- Actual outcome: All-cause mortality at Median 1.8 years; HR 0.78 (95%CI 0.63 to 0.96) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study	Hohnloser 2012[275]
Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Stroke or systemic embolism at Median 1.8 years; HR 0.61 (95%CI 0.39 to 0.94) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: acute or subacute clinically overt bleeding accompanied by one or more of the following: a decrease in the haemoglobin level of ≥2g/dL over a 24 our period; a transfusion of ≥2U f packed red blood cells; and/or bleeding that is fatal or occurs in at least one of the following critical sites: intracrnial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal. at Median 1.8 years; HR 0.48 (95%CI 0.37 to 0.64) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

Table 138: James 2010

Study	James 2010[312]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3237 with CrCl < 60 ml/min. (Total study n=15202))
Countries and setting	Conducted in Multiple countries; Setting: Hospitals
Line of therapy	1st line
Duration of study	Follow up (post intervention): Median duration of study treatment 9.1 months; follow up 360 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Creatinine level; creatinine clearace calculated with Cockcroft-Gault formula

Study	James 2010[312]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised for potential STE or non-STE ACS; onset in previous 24 hours
Exclusion criteria	Fibrinolytic therapy within 24 hours; need for oral anticoagulation therapy; need for dialysis; clinically important anaemia or thrombocytopaenia
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): 74 (68, 79). Gender (M:F): 39.8% female. Ethnicity: 88.5% White; 1.5% Black; 7.6% Oriental; 2.3% Other
Further population details	1. Older people aged 75 or over: Mixed (Median 74, IQR 68 to 79). 2. People with cardiovascular disease: People with cardiovascular disease (Hospitalised with acute coronary syndrome).
Extra comments	CKD population was a subgroup of full study - demographics of this subgroup aren't provided. . Randomisation not stratified for renal function
Indirectness of population	No indirectness
Interventions	(n=1619) Intervention 1: Antiplatelet agents - Ticagrelor. Loading dose 180mg then 90mg twice daily. Duration Median 9.1 months. Concurrent medication/care: Aspirin 75-100mg daily recommended but up to 325mg allowed for 6 months after stent placement Comments: Number randomised unclear - 1619 is around half the total of 3237 (n=1618) Intervention 2: Antiplatelet agents - Clopidogrel. If no clopidogrel in last 5 days: 300mg loading dose then 75mg daily; if previous clopidogrel: 75mg daily. Duration Median 9.1 months. Concurrent medication/care: Aspirin 75-100mg daily recommended but up to 325mg allowed for 6 months after stent placement Comments: Number randomised not stated: 1618 is around half of total 3237
Funding	Study funded by industry (AstraZeneca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL	

Study	James 2010[312]
Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum - Actual outcome: All-cause mortality at 1 year; HR 0.64 (95%CI 0.5 to 0.81) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Cardiovascular mortality or MI or stroke at 1 year; HR 0.71 (95%CI 0.59 to 0.86) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Major bleeding (PLATO defined) at 1 year; HR 1.08 (95%CI 0.87 to 1.34) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

Table 139: Jardine 2010, (Ruilope 2001)

Study (subsidiary papers)	Jardine 2010[315] (Ruilope 2001[597])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3083)
Countries and setting	Conducted in Multiple countries; Setting: 26 countries in Europe, North and South America and Asia
Line of therapy	1st line
Duration of study	Intervention time: Mean 3.8 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum creatinine; eGFR calculated using MDRD equation
Stratum	Overall

Study (subsidiary papers)	Jardine 2010[315] (Ruilope 2001[597])
Subgroup analysis within study	Not applicable: Baseline eGFR ≥60, 45-50 and <45
Inclusion criteria	Age 50-80 years; diastolic BP 100-115mmHg
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 61.3 (50-80). Gender (M:F): 67% female. Ethnicity: Not stated
Further population details	1. Older people aged 75 or over: Mixed (Age range 50-80 years). 2. People with cardiovascular disease: Mixed (All had hypertension (diastolic BP 100-115mmHg), 289 suffered a stroke, 349 had an myocardial infarction, 1005 had other coronary heart disease).
Extra comments	Median eGFR of 73 ml/min/1.73m^2. 14 978 had an eGFR ≥60, 3083 had an eGFR of 45-59 and 536 had an eGFR of <45 ml/min/1.73m^2. Diabetes: 9%, Previous MI: 1.8%, other coronary heart disease: 6.7%, previous stroke: 1.8%. . All participants were hypertensive (diastolic BP 100-115mmHg)
Indirectness of population	No indirectness
Interventions	(n=9308) Intervention 1: Antiplatelet agents - Aspirin. 75mg daily. Duration Mean 3.8 years. Concurrent medication/care: All had antihypertensive treatment (n=9289) Intervention 2: Placebo. Placebo. Duration Mean 3.8 years. Concurrent medication/care: All had antihypertensives
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus PLACEBO

Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum
- Actual outcome: Cardiovascular mortality at 3.8 years; HR 0.95 (95%CI 0.75 to 1.21) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: Cardiovascular mortality GFR≥60 at 3.8 years; HR 1.08 (95%CI 0.81 to 1.43) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome: Cardiovascular mortality GFR <45 at 3.8 years; HR 0.36 (95%CI 0.14 to 0.9) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Jardine 2010[315] (Ruilope 2001[597])
- Actual outcome: Cardiovascular mortality GFR 45-59 at 3.8 years; HR 0.92 (95%CI 0.54 to 1.54) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality at 3.8 years; HR 0.93 (95%CI 0.79 to 1.09) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality GFR ≥60 at 3.8 years; HR 1 (95%CI 0.83 to 1.2) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality GFR 45-59 at 3.8 years; HR 0.89 (95%CI 0.6 to 1.31) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: All-cause mortality GFR <45 at 3.8 years; HR 0.51 (95%CI 0.27 to 0.94) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: Myocardial infarction at 3.8 years; HR 0.71 (95%CI 0.58 to 0.88) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Major cardiovascular disease GFR≥60 at 3.8 years; HR 0.91 (95%CI 0.76 to 1.09) Reported; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Major cardiovascular disease GFR 45-59 at 3.8 years; HR 0.85 (95%CI 0.61 to 1.17) Reported; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Major cardiovascular disease GFR <45 at 3.8 years; HR 0.85 (95%CI 0.73 to 0.98) Reported; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Myocardial infarction GFR≥60 at 3.8 years; HR 0.78 (95%CI 0.61 to 1) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Myocardial infarction GFR 45-59 at 3.8 years; HR 0.64 (95%CI 0.39 to 1.03) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Myocardial infarction GFR <45 at 3.8 years; HR 0.31 (95%CI 0.11 to 0.85) Reported; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: Stroke at 3.8 years; HR 0.99 (95%CI 0.78 to 1.24) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Stroke GFR≥60 at 3.8 years; HR 1.09 (95%CI 0.83 to 1.44) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Stroke GFR 45-59 at 3.8 years; HR 1.02 (95%CI 0.64 to 1.62) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Stroke GFR <45 at 3.8 years; HR 0.31 (95%CI 0.11 to 0.85) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Myocardial infarction GFR <45 at 3.8 years; HR 0.31 (95%CI 0.11 to 0.85) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Major bleeding (fatal, life-threatening, disabling or requiring hospital admission) at 3.8 years; HR 1.61 (95%CI 1.21 to 2.14) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Major bleeding (fatal, life-threatening, disabling or requiring hospital admission) GFR ≥60 at 3.8 years; HR 1.52 (95%CI 1.11 to 2.08) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	

Study (subsidiary papers)	Jardine 2010[315] (Ruilope 2001[597])
- Actual outcome: Major bleeding (fatal, life-threatening, disabling or requiring hospital admission) GFR 45-59 at 3.8 years; HR 1.7 (95%CI 0.74 to 3.88) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Major bleeding (fatal, life-threatening, disabling or requiring hospital admission) GFR <45 at 3.8 years; HR 1.61 (95%CI 1.21 to 2.14) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: Minor bleeding (as reported by the studies) (Important) at Define - Actual outcome: Minor bleeding at 3.8 years; HR 1.7 (95%CI 1.28 to 2.25) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Minor bleed GFR ≥60 at 3.8 years; HR 1.54 (95%CI 1.11 to 2.13) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Minor bleed GFR 45-59 at 3.8 years; HR 2.25 (95%CI 1.22 to 4.14) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Minor bleed GFR <45 at 3.8 years; HR 2.57 (95%CI 0.5 to 13.27) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 140: Keltai 2007

Study	Keltai 2007[334]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4087)
Countries and setting	Conducted in Multiple countries; Setting: Hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean 9 months treatment; outcomes at 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum creatinine and eGFR calculated using MDRD formula
Stratum	Overall

Study	Keltai 2007[334]
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-STE ACS; hospitalised within 24 hours of symptoms; positive troponin or creatine kinase-MB levels; or ischaemic changes on ECG other than ST elevation of 2mm or more
Exclusion criteria	Contraindications to antithrombotic or antiplatelet therapy; high risk for bleeding; administration of oral anticoagulants; coronary revascularisation in last 3 months; IV glycoprotein IIb/IIIa inhibitors in previous 3 days; planned long term (>3 months) administration of NSAIDs
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 69.6 (9.9). Gender (M:F): 51.2% female. Ethnicity: Not stated
Further population details	1. Older people aged 75 or over: Mixed (Mean 69.6 (9.9) years). 2. People with cardiovascular disease: People with cardiovascular disease (All acute coronary syndrome).
Extra comments	History: MI; 32.23%, CABG;11%, PCI; 9.9%, Stroke; 4%, peripheral arterial disease; 8.4%, heart failure; 7.6%, hypertension; 58.9%, diabetes; 22.6%.. People in the lowest tertile of eGFR were significantly older, more often female and had more frequent comorbid conditions. Previous MI, stroke, peripheral arterial disease, heart failure, hypertension and diabetes were more prevalent in this group.
Indirectness of population	Serious indirectness: All participatns had acute coronary syndrome (ACS) without ST-segment elevation. (Subgroup analysis of people with CKD).
Interventions	(n=2044) Intervention 1: Antiplatelet agents - Clopidogrel. Loading dose 300mg then 75mg daily for 3-12 months. Duration mean duration 9 months. Concurrent medication/care: Aspirin 75-325mg daily recommended Comments: Number randomised not stated: 2044 is around half the 4087 total (n=2043) Intervention 2: Placebo. placebo. Duration Mean duration 9 months. Concurrent medication/care: Aspirin 75-325mg daily recommended Comments: Number randomised not stated: 2043 is around half the 4087 total
Funding	Study funded by industry (Bristol-Myers Squibb, Sanofi-Synthelabo)

Study	Keltai 2007[334]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus PLACEBO Protocol outcome 1: Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum - Actual outcome: All-cause mortality at 1 year; Mean 0.95 (95%CI 0.78 to 1.16); Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Cardiovascular mortality at 1 year; Mean 0.95 (95%CI 0.77 to 1.17); Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Major bleeding (as reported by studies) (Critical) at 6 months minimum - Actual outcome: Bleeding (life-threatening) at 1 year; Mean 0.89 (95%CI 0.6 to 1.31); Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome: Major bleeding at 1 year; Mean 1.37 (95%CI 0.89 to 2.12); Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 3: Minor bleeding (as reported by the studies) (Important) at Define - Actual outcome: Minor bleeding at 1 year; Mean 1.50 (95%CI 1.21 to 1.86); Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular or cerebrovascular events (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 141: Mega 2012

Study	Mega 2012[440]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=15526)
Countries and setting	Conducted in Multiple countries; Setting: 766 sites in 44 countries
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 13.1 months

Study	Mega 2012[440]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Creatinine clearance above or below 50ml/min
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: ACS; subgroup with renal impairment
Inclusion criteria	≥18 years of age; symptoms suggestive of an acute coronary syndrome and in whom STEMI, NSTEMI or unstable angina diagnosed; those under 55 years had either diabetes mellitus or a previous MI in addition to the index event
Exclusion criteria	platelet count <90,000/mm3, haemoglobin <10g/dL, or a creatinine clearance <30ml/min at screening; clinically significant gastrointestinal bleeding within 12 months before randomization; previous intracranial haemorrhage; previous ischemic stroke or TIA in patients who were taking both aspirin and a thienopyridine
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 61.8±9.2 for rivaroxaban 2.5mg; 61.9±9.0 for rivaroxaban 5mg; 61.5±9.4 for placebo. Gender (M:F): 11600:3926. Ethnicity: White 11409; Black 107; Asian 3229; Other 781
Further population details	1. Older people aged 75 or over: Mixed 2. People with cardiovascular disease: People with cardiovascular disease (ACS; subgroup with renal impairment).
Indirectness of population	Serious indirectness: ACS patients; subgroup by renal impairment
Interventions	(n=5174) Intervention 1: Oral anticoagulants - Rivaroxaban. Rivaroxaban 2.5mg twice daily. Duration 13.1 months. Concurrent medication/care: Aspirin 5105/5174 (98.7%); Thienopyridine 4790 (92.6%); Beta-blocker 3426 (66.2%); ACE inhibitor or ARB 2022 (39.1%); Statin 4304 (83.2%); Calcium channel blocker 820 (15.8%) (n=5176) Intervention 2: Oral anticoagulants - Rivaroxaban. Rivaroxaban 5mg twice daily. Duration 13.1 months. Concurrent medication/care: Aspirin 5099/5176 (98.5%); Thienopyridine 4812 (93.0%); Beta-blocker 3394 (65.6%); ACE inhibitor or ARB 1977 (38.2%); Statin 4342 (83.9%); Calcium channel blocker 742 (14.3%) (n=5176) Intervention 3: Placebo. Placebo. Duration 13.1 months. Concurrent medication/care: Aspirin 5108/5176 (98.7%); Thienopyridine 4811 (92.9%); Beta-blocker 3444 (66.5%); ACE inhibitor or ARB 2050 (39.6%); Statin 4321 (83.5%); Calcium channel blocker 764 (14.8%)

Study	Mega 2012[440]
Funding	Study funded by industry (Johnson & Johnson and Bayer Healthcare)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN versus PLACEBO Protocol outcome 1: Cardiovascular or cerebrovascular events (Critical) at 6 months minimum - Actual outcome: CV death, MI or stroke (creatinine clearance <50ml/min) at 13.1 months; Group 1: 80/686, Group 2: 49/368; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Important) at 6 months minimum; Progression of CKD (change in eGFR) (Important) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Major bleeding (as reported by studies) (Critical) at 6 months minimum; Minor bleeding (as reported by the studies) (Important) at Define; Health related quality of life (Important) at 6 months minimum

G.11 Asymptomatic hyperuricaemia

Study	Goicoechea 2010[230]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in Spain; Setting: Outpatient
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: estimated GFR and serum creatinine
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Renal disease (eGFR <60), no hospitalisations or cardiovascular events in last 3 months, baseline serum creatinine not increased by 50% in previous 3 months
Exclusion criteria	History of allopurinol intolerance, already on allopurinol treatment, active infection or inflammatory diseases, HIV infection, chronic hepatopathy, immunosuppressive therapy
Age, gender and ethnicity	Age - Mean (SD): Intervention group: 72.1 (7.9) Control group: 71.4 (9.5). Gender (M:F): Not reported. Ethnicity:
Further population details	1. Aged 75 or older or under 75: Not applicable / Not stated / Unclear
Extra comments	People with "moderate" chronic kideny disease not already on allopurinol
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Uric acid lowering therapies - Allopurinol. 100mg, route oral. Duration 24 months. Concurrent medication/care: Usual treatment including antihypertensive agents and diuretics. (n=56) Intervention 2: Usual care - Usual care (as defined by study). Continued on usual treatment (no further details). Duration 24 months. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus USUAL CARE (AS DEFINED BY STUDY)

Protocol outcome 1: Hospitalisation at 3 months
- Actual outcome: Hospitalisation at 24 months; Group 1: 12/54, Group 2: 22/50; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Cardiovascular events at 3 months
- Actual outcome: Congestive HF, ischaemic coronary events, cerebrovascular accidents, peripheral arteriopathy, arrhythmia at 24 months; Group 1: 7/57, Group 2: 15/56; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Renal progression - eGFR (final values) at 3 months
- Actual outcome: eGFR at 24 months; Group 1: mean 42.2 ml/min/1.73m2 (SD 13.2); n=54, Group 2: mean 35.9 ml/min/1.73m2 (SD 12.3); n=50; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Renal progression - end stage renal disease needing RRT at 3 months - Actual outcome: Dialysis at 24 months; Group 1: 1/57, Group 2: 1/56; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: All cause mortality at 3 months - Actual outcome: Mortality at 24 months; Group 1: 0/57, Group 2: 2/56; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Reduction in antihypertensive agents at 3 months; Serious adverse events at 3 months; Cardiovascular mortality at 3 months; Quality of life at 3 months

Study	Kao 2011[328]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR 30 to 60ml/min/1.73m2
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Stage 3 CKD; left ventricular hypertrophy
Exclusion criteria	Not stated
Recruitment/selection of patients	Recruited from General Nephrology clinic and Cardiovascular Risk clinic, January to December 2008
Age, gender and ethnicity	Age - Mean (SD): Intervention: 70.6 ± 6.9 years; control: 73.7 ± 5.3 years. Gender (M:F): 28:25. Ethnicity: Not stated
Further population details	1. Aged 75 or older or under 75:
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Uric acid lowering therapies - Allopurinol. 300mg once a day orally. Duration 9 months. Concurrent medication/care: Not stated (n=35) Intervention 2: Placebo. Placebo. Duration 9 months. Concurrent medication/care: Not stated
Funding	Academic or government funding (British Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus PLACEBO

Protocol outcome 1: Reduction in antihypertensive agents at 3 months
- Actual outcome: Antihypertensive agents stopped at 9 months; Group 1: 5/27, Group 2: 2/26; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Renal progression - eGFR (final values) at 3 months - Actual outcome: Change in eGFR at 9 months; Group 1: mean 0.2 ml/min/1.73m2 (SD 6.9); n=27, Group 2: mean 0.2 ml/min/1.73m2 (SD 5.5); n=26; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All cause mortality at 3 months - Actual outcome: All cause mortality at 9 months; Group 1: 0/32, Group 2: 1/35; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 3 months; Cardiovascular events at 3 months; Renal progression - end stage renal disease needing RRT at 3 months; Serious adverse events at 3 months; Cardiovascular mortality at 3 months; Quality of life at 3 months

Study	Siu 2006[637]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in China; Setting: Secondary care
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Serum uric acid level >7.6mg/dL
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Daily proteinuria > 0.5g and/or elevated sCr >120µmol/L; baseline sCr level and daily proteinuria not increased by >40% within last 3 months; uric acid level >452 µmol/L
Exclusion criteria	History of gouty arthritis; renal stones; advanced CKD (sCr >400 µmol/L); patients already on allopurinol or azathioprine; known allopurinol hypersensitivity; women of childbearing age who were unwilling to use "effective means" of contraception; pregnancy or lactation
Recruitment/selection of patients	Renal clinic fron April 2003 to April 2004
Age, gender and ethnicity	Age - Mean (SD): Allopurinol: 47.7 (12.9); control: 48.8 (16.8) years. Gender (M:F): 19:22. Ethnicity: Not stated
Further population details	1. Aged 75 or older or under 75:
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Uric acid lowering therapies - Allopurinol. Allopurinol 100mg to 300mg once a day orally. Duration 12 months. Concurrent medication/care: Not stated (n=28) Intervention 2: Usual care - Usual care (as defined by study). Usual care (no futher details). Duration 12 months. Concurrent medication/care: Not stated
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus USUAL CARE (AS DEFINED BY STUDY) Protocol outcome 1: Reduction in antihypertensive agents at 3 months - Actual outcome: Reduction in antihypertensive agents (ACEI and ARBs) at 12 months; Group 1: 0/23, Group 2: 0/19; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Renal progression - end stage renal disease needing RRT at 3 months - Actual outcome: End stage renal failure at 12 months; Group 1: 1/25, Group 2: 1/26; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: All cause mortality at 3 months - Actual outcome: Mortality at 12 months; Group 1: 0/25, Group 2: 0/26; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 3 months; Cardiovascular events at 3 months; Renal progression - eGFR (final values) at 3 months; Serious adverse events at 3 months; Cardiovascular mortality at 3 months; Quality of life at 3 months

G.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

Table 142: Baker 1989

Study	Baker 1989[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in United Kingdom
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 mths
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: creatinine clearance
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with creatinine clearance 20 to 60 ml/min
Exclusion criteria	Pregnancy, hypertension, gastrointestinal or liver disease, urinary protein output greater than 3 g daily, psychosis, known tetracycline allergy, treatment with medication known to affect bone, or vitamin D metabolites
Age, gender and ethnicity	Age - --: . Gender (M:F): 7:6. Ethnicity: not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Older people aged 75 or over: Aged under 75 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism (7/13 had elevated concentrations of parathyroid hormone).
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Vitamin D - Calcitriol (1,25 dihidroxycholecalciferol). 0.25 ug daily increaed to twice daily if serum calcium below 2.6 mmol/L. Duration 12 mths. Concurrent medication/care: anti-hypertensives. Phosphate binders in one patient. Calcium supplementation as required. Continued on usual diet. (n=8) Intervention 2: Placebo. no details. Duration 12 mths. Concurrent medication/care: As for intervention

Study	Baker 1989[51]
Funding	Study funded by industry (Dialysis Clinics Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCITRIOL (1,25 DIHIDROXYCHOLECALCIFEROL) versus PLACEBO Protocol outcome 1: Cardiovascular events (Critical) at 6 months minimum - Actual outcome: Incidence of myocardial infarction at 12 mths; Group 1: 0/8, Group 2: 1/8; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: > 2.6 mmol/L at 12 mths; Group 1: 4/7, Group 2: 0/5; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Progression of CKD (change in eGFR) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 143: Coburn 2004

Study	Coburn 2004[133]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=55)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 24 weeks

Study	Coburn 2004[133]
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-85 years; serum creatinine 1.8-5.0mg/dL for men or 1.6-4.0mg/dL for women; plasma iPTH >85pg/ml
Exclusion criteria	Alcohol or drug abuse; pregnancy or nursing; history of nephrolithiasis, renal transplant, hyperthyroidism or sarcoidosis; active malignancy requiring treatment; gastrointestinal disease (e.g. malabsorption syndrome, surgery that might reduce intestinal absorption, ulcerative colitis); significant impairment of hepatic function; any other condition that might place patient at undue risk or preclude study completion; treatment with anticonvulsants, glucocorticoids, bisphosphonates, fluoride or lithium in previous 12 months.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 64.1 (12.6) doxercalciferol; 65.0 (12.1) placebo. Gender (M:F): 45 male; 10 female. Ethnicity: 28/55 Caucasian; 22 African American; 4 Hispanic; 1 Other
Further population details	1. Black and minority ethnic groups: RCT mixed population (28/55 Caucasian; 22 African American; 4 Hispanic; 1 Other). 2. Older people aged 75 or over: Mixed (Age 18-85 years). 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism (CKD stage 3 or 4 and secondary hyperparathyroidism).
Extra comments	Stage 3 or 4 chronic kidney disease and secondary hyperparathyroidism. None
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Vitamin D - Doexercalciferol. 2 capsules (0.5microg each) daily before breakfast; increased by 1 capsule per day at monthly intervals if plasma iPTH not reduced by at least 30% from baseline, and providing serum calcium 9.6mg/dL or less, serum phosphorus 5.0mg/dL or less, 24 hour urinary calcium 200mg or less and fasting urine calcium-creatinine ratio 0.25mg/mg or less; maximum dose 10 capsules/day (5microg). Duration 24 weeks. Concurrent medication/care: Only calcium-based phosphate binders were administered (n=28) Intervention 2: Placebo. 2 capsules daily before breakfast; increased by 1 capsule per day at monthly intervals if plasma iPTH not reduced by at least 30% from baseline, and providing serum calcium 9.6mg/dL or less, serum phosphorus 5.0mg/dL or less, 24 hour urinary calcium 200mg or less and fasting urine calcium-creatinine ratio

Study	Coburn 2004[133]
	0.25mg/mg or less; maximum dose 10 capsules/day . Duration 24 weeks. Concurrent medication/care: Only calcium-based phosphate binders were administered
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOEXERCALCIFEROL versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 6 months minimum - Actual outcome: mean mGFR at 24 weeks; Group 1: mean 30 ml/min (SD 13.6); n=22, Group 2: mean 33.9 ml/min (SD 14.76); n=20; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: Hypercalcaemia (>2.67mmol/L) at 24 weeks; Group 1: 1/27, Group 2: 1/28; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 144: Coyne 2006

Study	Coyne 2006[143]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=220 (107 intervention, 113 placebo))
Countries and setting	Conducted in Poland, USA; Setting: 46 investigative sites.
Line of therapy	Adjunctive to current care

Study	Coyne 2006[143]
Duration of study	Intervention + follow up: 24 weeks intervention plus 30 day follow up for adverse events
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR by MDRD
Stratum	Overall: N/A
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older, diagnosed with CKD for longer than 2 months, and had not been on active vitamin D therapy in the previous 4 weeks. eGFR 15-60 ml/min/1.73m^2 who were not expected to begin dialysis therapy for at least 6 months. People who had been administered a phosphate binder were to have been on a stable regimen for at least 4 weeks before the screening visit.
Exclusion criteria	Acute renal failure in the past 12 weeks, clinically significant chronic gastrointestinal disease or liver disease, malignancy, active granulomatous disease (tuberculosis, sarcoidosis etc.), pregnancy, history of hypersensitivity to vitamin D, spot urinary calcium-creatinine ratio greater than 0.2, or history of renal stones. People were also excluded if they were administered medications that could potentially affect calcium or bone metabolism, such as calcitonin or bisphosphonates, or if they had been administered glucocorticoids for more than 14 days within 6 months. Aluminium containing phosphate binders were not allowed for more than 3 weeks during the study.
Recruitment/selection of patients	The randomisation schedule was computer generated before the study began by Abbott. At the start of the treatment phase, eligible participants were assigned a unique 4-digit number in ascending numerical sequence per investigative site, which randomly asigned them to treatment with paricalcitol or placebo. Studies were performed in 4 parts: a screening visit, pretreatment phase, treatment phase, and follow-up phase. At the screening visit, blood samples were collected for iPTH, blood urea nitrogen, albumin, and serum creatinine levels, and the patient's estimated GFR was derived. During the pretreatment phase (1-4 weeks) patients had 2 visits with blood draws at least 1 day apart. If they had 2 consecutive iPTH levels averaging 150pg/ml or greater and 2 consecutive phosphorus levels of 5.2mg/dl or less, they were eligible to enter the treatment phase.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 63.6 (13.2) Placebo: 61.8 (12.4). Gender (M:F): 67.5% male. Ethnicity: 71% white, 26% black 3% other (no difference between groups)
Further population details	1. Black and minority ethnic groups: RCT mixed population 2. Older people aged 75 or over: Mixed (Range not stated). 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism
Extra comments	Baseline eGFR (ml/min/1.73m^2), mean (SD) Intervention: 23.1 (8.1), Placebo 23 (7.8). Baseline eGFR (ml/min/1.73m^2),

Study	Coyne 2006[143]
	mean (SD) Intervention: 23.1 (8.1), Placebo 23 (7.8)
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Vitamin D - Paracalcitrol. The initial dose was determined according to baseline iPTH levels. In the thrice weekly studies, dosing was initiated at 2µg thrice weekly for baseline iPTH of 500pg/ml or les or 4µg if iPTH >500pg/ml. In the once daily study, the initial dose was 1µg once daily if baseline iPTH level was 500pg/ml or less and 2µg if iPTH >500pg/ml. Subsequent doses were titrated by 2µg for thrice weekly studies and 1µg for once daily studies. Dose increases could occur evey 4 weeks until a 30% decrease in iPTH levels was achieved. The dose could be decreased every 2 weeks or sooner if iPTH level was decreased by greater than 60% from baseline, serum calcium level was elevated, or serum phosphorus level was persistently elevated.. Duration 24 weeks. Concurrent medication/care: Patients on phosphate binder therapy were to maintain a stable regimen (brand and doses) throughout treatment. Comments: Patients were discontinued from the study if they required dialysis therapy, or if after 4 weeks of therapy, 2 consecutive iPTH values were greater than 1000pg/ml or were at least 3-fold greater than baseline. (n=113) Intervention 2: Placebo. Placebo capsules were similar to paricalcitol capsules in size, colour, shape and contents, with absence of the active drug.. Duration 24 weeks. Concurrent medication/care: As for intervention group Comments: Patients were discontinued from the study if they required dialysis therapy, or if after 4 weeks of therapy, 2 consecutive iPTH values were greater than 1000pg/ml or were at least 3-fold greater than baseline.
Funding	Study funded by industry (Abbott Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACALCITROL versus PLACEBO

Protocol outcome 1: Mortality (all cause) (Critical) at 6 months minimum
- Actual outcome: Deaths (reported within adverse events) at 7 months; Group 1: 2/107, Group 2: 1/113; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 2: Progression of CKD (change in eGFR) (Critical) at 6 months minimum
- Actual outcome: Change from baseline in eGFR (measured by MDRD) at 24 weeks; Group 1: mean 21.4 ml/min/1.73m^2 (SD 8.96); n=82, Group 2: mean 21.9

Study	Coyne 2006[143]
ml/min/1.73m^2 (SD 8.97); n=93; Risk of bias: --; Indirectness of outcome: No indirectness Protocol outcome 3: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: At least 2 consecutive correctied calcium vales >2.62mmol/l) at 24 weeks; Group 1: 2/107, Group 2: 0/113; Risk of bias: --; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 145: Hamdy 1995

Study	Hamdy 1995[245]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=176)
Countries and setting	Conducted in Belgium, France, Netherlands, United Kingdom
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 yrs
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: creatinine clearance
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Creatinine clearance 15-50 ml/min and no evidence of renal bone disease
Exclusion criteria	A raised serum calcium concentration or total alkaline phosphatase activity, and disturbance in liver function.
Age, gender and ethnicity	Age - Mean (SD): vit D 53 (15) placebo 51 (16). Gender (M:F): % male Exptl 61% control 61%. Ethnicity: Not stated

Study	Hamdy 1995[245]
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Older people aged 75 or over: Systematic review: mixed 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism (Elevated para thyroid hormone 50/72).
Indirectness of population	No indirectness
Interventions	(n=89) Intervention 1: Vitamin D - Alfacalcidol (1 alpha hydroxycholecalciferol). 0.25 µg daily increasing to 1 µg a day in order to maintain serum calcium concentration at the upper limit of normal lab reference range. Duration 2 yrs. Concurrent medication/care: The use of phosphate binding drugs other than calcium was permitted when dietary restriction of phosphate failed to maintain serum phosphate concentrations below 2.2 mmol/l (n=87) Intervention 2: Placebo. Placebo. Duration 2 yrs. Concurrent medication/care: The use of phosphate binding drugs other than calcium was permitted when dietary restriction of phosphate failed to maintain serum phosphate concentrations below 2.2 mmol/l
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALFACALCIDOL (1 ALPHA HYDROXYCHOLECALCIFEROL) versus PLACEBO Protocol outcome 1: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: > 2.63 mmol/l at 2 yrs; Group 1: 14/89, Group 2: 3/87; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Progression of CKD (creatinine clearance) at Define - Actual outcome: creatinine clearance ml/min at 2 yrs; Group 1: mean -5.9 ml/min (SD 9.4); n=89, Group 2: mean -4 ml/min (SD 18.7); n=87; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Progression of CKD (change in eGFR) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 146: Nordal 1988

Study	Nordal 1988[490]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Norway
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 8 mths
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: serum creatinine 180 umol/L
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Serum creatinine greater thn 180 umol/L and stable renal function for the previous 4 mths
Exclusion criteria	None stated
Age, gender and ethnicity	Age - Range: vit D 26-71 placebo 23-69. Gender (M:F): Vit D 9:6 placebo 11:4. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Older people aged 75 or over: Aged under 75 3. People with secondary hyperparathyroidism: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Vitamin D - Calcitriol (1,25 dihidroxycholecalciferol). 0.25 ug once daily rising to twice daily. Duration 8 mths. Concurrent medication/care: Phosphate binding agents allowed (n=15) Intervention 2: Placebo. no details. Duration 8 mths. Concurrent medication/care: as for intervention
Funding	Academic or government funding (Placebo tablets from Hoffman La Roche.)

Study	Nordal 1988[490]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCITRIOL (1,25 DIHIDROXYCHOLECALCIFEROL) versus PLACEBO Protocol outcome 1: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: > 2.7 mmol/L at 8 mths; Group 1: 8/14, Group 2: 0/14; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Progression of CKD (change in eGFR) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 147: Patel 2011

Study	Patel 2011[532]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=24)
Countries and setting	Conducted in USA; Setting: Nephrology centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	CKD stage 3 or 4; serum 25(OH)D 30ng/ml or more; iPTH >110 and <450pg/ml for stage 3 and >150 and <450 for stage 4
Exclusion criteria	Serum calcium >9.5mg/dL; phosphorus>4.6mg/dL; spot urine calcium/creatinine ratio >0.2; spot urine protein/creatinine ratio >3.5; any clinically significant unstable medical condition

Study	Patel 2011[532]
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 66.7 (14) placebo; 67.4 (11) doxercalciferol. Gender (M:F): 16 male, 8 female. Ethnicity: 17/24 White; 4 Black/African American; 3 Other
Further population details	1. Black and minority ethnic groups: RCT mixed population (17/24 White; 4 Black/African American; 3 Other). 2. Older people aged 75 or over: Mixed (Age over 18 years). 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism (CKD stage 3 or 4 and secondary hyperparathyroidism).
Extra comments	Vitamin D replete patients with CKD stage 3 or 4 and secondary hyperparathyroidism. None
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Vitamin D - Doexercalciferol. 2 capsules (1microg) daily; titrations of 1 capsule daily at 2-week intervals to achieve iPTH levels <70pg/ml for stage 3 and <110pg/ml for stage 4 patients. Duration 24 weeks. Concurrent medication/care: Patients advised to maintain constant dietary intake of calcium and phosphorus, and current dose of phosphate binder during study (n=12) Intervention 2: Placebo. 2 capsules daily, titrated by 1 capsule daily at 2-week intervals. Duration 24 weeks. Concurrent medication/care: Patients advised to maintain constant dietary intake of calcium and phosphorus, and current dose of phosphate binder during study
Funding	Study funded by industry (Genzyme)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOEXERCALCIFEROL versus PLACEBO

Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 6 months minimum
- Actual outcome: median change in eGFR from baseline to week 24 at 24 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum
- Actual outcome: Hypercalcaemia (level not specified) at 24 weeks; Group 1: 0/12, Group 2: 0/12; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Patel 2011[532]
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 148: Przedlacki 1995

Study	Przedlacki 1995[557]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in Finland
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 mths
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GFR
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	GFR equal or below 51.2 ml/min and age below 70 yrs
Exclusion criteria	Pregnancy, hypercalcemia (serum > 2.6 mmol/l), renal stones, intestinal diseases, diabetes, treatment with steroids and vit D metabolites, anticoagulants, anticonvulsants
Age, gender and ethnicity	Age - Other: range 35-64. Gender (M:F): vit D 2:13 placebo 8:4. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Older people aged 75 or over: Not applicable / Not stated / Unclear 3. People with secondary hyperparathyroidism: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Vitamin D - Calcitriol (1,25 dihidroxycholecalciferol). 0.25 µg/day. Duration 12 mths.

Study	Przedlacki 1995[557]
	Concurrent medication/care: Depending on age, patients were on a low protein and low phosphorus diet. Some of them received calcium carbonate or aluminium-containing phosphorus binders before the study (n=13) Intervention 2: Placebo. Placebo. Duration 12 mths. Concurrent medication/care: Depending on age, patients were on a low protein and low phosphorus diet. Some of them received calcium carbonate or aluminum-containing phosphorus binders before the study
Funding	Study funded by industry (Hoffman La Roche)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCITRIOL (1,25 DIHIDROXYCHOLECALCIFEROL) versus PLACEBO Protocol outcome 1: Fracture (Critical) at 6 months minimum - Actual outcome: Incidence of fracture at 12 mths; Group 1: 0/13, Group 2: 1/12; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: > 2.6 mmol/litre at 12 months; Group 1: 2/13, Group 2: 0/12; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Mortality (cardiovascular) (Critical) at 6 months minimum - Actual outcome: Incidence of myocardial infarction reported at 12 months; Group 1: 0/13, Group 2: 1/13; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Progression of CKD (change in eGFR) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

Table 149: Ritz 1995

Study	Ritz 1995[572]

Study	Ritz 1995[572]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in Germany
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 18 mths
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: serum creatinine
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Serum creatinine above 1.4 mg/dl and below 6.5 mg/dl 1,84 iPTH levels above the normal range ie 6 pmol/l on three separate occasions during recruitment
Exclusion criteria	Nephrotic proteinuria, diabetes mellitus, immunosuppressive therapy, frank vit D deficiency, anticonvulsive therapy and mephrocalcinosis
Age, gender and ethnicity	Age - Mean (SD): Vit D 55 placevo 54. Gender (M:F): vit D 10:11 placebo 16:8. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Older people aged 75 or over: Aged under 75 3. People with secondary hyperparathyroidism: CKD and secondary hyperparathyroidism
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Vitamin D - Calcitriol (1,25 dihidroxycholecalciferol). 0.125 µg. Duration 12 mths. Concurrent medication/care: Calcium carbonate if serum phosphate exceeded 1.7 mmol/l (n=21) Intervention 2: Placebo. dose/quantity, brand name, extra details. Duration 12 mths. Concurrent medication/care: Not specified
Funding	Funding not stated (No funding stated)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCITRIOL (1,25 DIHIDROXYCHOLECALCIFEROL) versus PLACEBO	

Study	Ritz 1995[572]
Protocol outcome 1: Hypercalcaemia (serum calcium >2.5 mmol/litre) (Critical) at 6 months minimum - Actual outcome: > 2.7 mmol/l at 12 mths; Group 1: 0/24, Group 2: 0/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all cause) (Critical) at 6 months minimum; Cardiovascular events (Critical) at 6 months minimum; Fracture (Critical) at 6 months minimum; Progression of CKD (change in eGFR) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Mortality (cardiovascular) (Critical) at 6 months minimum; Progression of CKD (creatinine clearance) at Define; Health related quality of life (Important) at 6 months minimum

G.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

Table 150: De brito-ashurst 2009

Study	De brito-ashurst 2009[155]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=134)
Countries and setting	Conducted in United Kingdom; Setting: Single centre outpatients. The low-clearance clinic at the Royal London Hospital, part of the Barts and The London NHS Trust, UK.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 24 months52
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Creatinine clearance 15-30ml/min/1.73m^2 calculated from a 24 hour urine
Stratum	Overall: Stratified by gender and presence or absence of diabetes with block randomisation within each stratum.
Subgroup analysis within study	Stratified then randomised

Study	De brito-ashurst 2009[155]
Inclusion criteria	Age >18; stage 4-5 CKD; plasma bicarbonate <20 and >16mmol/L on two consecutive measurements; stable clinical condition.
Exclusion criteria	Malignant disease; morbid obesity; cognitive impairment; chronic sepsis; poorly controlled blood pressure (>150/90mmHg) despite use of four agents; overt congestive heart failure; steroid therapy.
Recruitment/selection of patients	Selected from patients already attending clinic by the principal investigator who was blind to group allocations until the end of the study. "Randomly assigned" to intervention or "routine standard care".
Age, gender and ethnicity	Age - Other: Mean (SE): Control: 54.8 (2.34); Bicarbonate: 54.8 (2.56). Gender (M:F): 69:65. Ethnicity: 52% white: 48% black/Asian
Further population details	1. Older people aged 75 or over: Not applicable / Not stated / Unclear
Extra comments	Adults with CrCl 15-30ml/min/1.73m^2 and serum bicarbonate 16-20mmol/L.
Indirectness of population	No indirectness
Interventions	(n=67) Intervention 1: Oral bicarbonate supplements - Sodium bicarbonate. 600mg orally three times a day increased as necessary to maintain bicarbonate level ≥23 mmol/L. Mean 1.82 ± 0.8g/day. . Duration 24 months. Concurrent medication/care: In all patients use of sevelemar hydrochloride was avoided; calcium acetate was the only phosphate binder allowed. (n=67) Intervention 2: Usual care. Standard treatment and monitoring of CKD. Duration 24 months. Concurrent medication/care: In all patients use of sevelemar hydrochloride was avoided; calcium acetate was the only phosphate binder allowed.
Funding	Academic or government funding (Barts and the London Charitable Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SODIUM BICARBONATE versus USUAL CARE

Protocol outcome 1: Cardiovascular events (including chronic heart failure) (Critical) at 6 months minimum
- Actual outcome: Worsening oedema requiring increase in loop diuretics at 24 months; Group 1: 26/67, Group 2: 20/67; Risk of bias: High; Indirectness of outcome: --

Study	De brito-ashurst 2009[155]
Protocol outcome 2: Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 6 months minimum - Actual outcome: End stage renal disease requiring RRT (CrCl <10ml/min) at 24 months; Group 1: 4/62, Group 2: 22/67; Risk of bias: High; Indirectness of outcome: -- Protocol outcome 3: Progression of CKD (change in eGFR) (Critical) at 6 months minimum - Actual outcome: Decline in creatinine clearance at 24 months; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 4: Hypertension (measured by use of antihypertensives) (Critical) at 6 months minimum - Actual outcome: Worsening hypertension requiring an increase in therapy at 24 months; Group 1: 41/67, Group 2: 32/67; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Hospitalisation (Important) at 6 months minimum - Actual outcome: Hospitalisation for congestive heart failure at 24 months; Group 1: 0/67, Group 2: 0/67; Risk of bias: Low; Indirectness of outcome: --	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Alkalosis (Critical) at 6 months minimum; Nutrition (measured by subjective global assessment) (Critical) at 6 months minimum; Nutrition (measured by change in BMI) (Critical) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Table 151: Mahajan 2010

Study	Mahajan 2010[408]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in USA; Setting: People identified from general clinical database of Texas Tech University Health Science Center. Follow up in outpatient internal medicine clinic.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 5 years

Study	Mahajan 2010[408]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eGFR 60-90ml/min by MDRD.
Stratum	Overall: Age, eGFR, albuminuria and ethnicity.
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Non-malignant hypertension; macroalbuminuria (Urine albumin >200 but <2000mg/g creatinine); eGFR ≥60 but <90ml/min; ≥2 clinic visits showing compliance; age ≥18 years and able to give consent.
Exclusion criteria	Known primary kideny disease or findings consistent thereof such as ≥3 red blood cells per high-powered field of urine or urine cellular casts; history of diabetes or fasting blood glucose ≥110mg/dl; history of malignancy, chronic infection, pregnancy, or clinical evidence of cardiovascular disease; peripheral oedema or diagnoses associated wityh oedema including heart/liver failure or nephrotic syndrome; smoking or oral tobacco use within 1 year of recruitment; history of medication non-compliance; frank metabolic acidosis (plasma total carbon dioxide <24.5mM). Clinically excluded people with systemic diseases associated with nephropathy, nephrotic proteinuria, and urine abnormalities other than albuminuria (none had renal biopsy). Clinically excluded secondary causes of hypertension such as renal artery stenosis or hyperaldosteronism (none had doppler studies or serum aldosterone:renin ratio).
Recruitment/selection of patients	491 people identified from database; 349 met inclusion criteria; 120 included in final study (40 in each arm: sodium bicarbonate, sodium chloride and placebo).
Age, gender and ethnicity	Age - Mean (SD): Bicarbonate: 51.2 (8.2); Placebo: 51.3 (8.5). Gender (M:F): 38:42. Ethnicity: 63% Black: 22% Hispanic: 15% White
Further population details	1. Older people aged 75 or over: Not applicable / Not stated / Unclear
Extra comments	Adults with eGFR 60-90ml/min (CKD Stage 2) and hypertensive nephropathy and macroalbuminuria..
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Oral bicarbonate supplements - Sodium bicarbonate. Sucrose + sodium bicarbonate tablets, each 10mEq. Dose 0.5mEq/kg lean body weight daily. Prescribed tablets to nearest half tablet (for example weight 70kg, dose 3.5 tablets).. Duration 5 years. Concurrent medication/care: Annual clinic visit, blood pressure control included an ACE inhibitor for all patients. (n=40) Intervention 2: Placebo. Matched placebo - sucrose tablet.. Duration 5 years. Concurrent medication/care:

Study	Mahajan 2010[408]
	Annual clinic visit, blood pressure control included an ACE inhibitor for all patients.
Funding	Academic or government funding (Larry and Jane Woirhaye Memorial Endowment in Renal research; Texas Tech University Health Sciences Center; Statistics Department of Texas A&M University; Research Division of Scott and White Healthcare.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SODIUM BICARBONATE versus PLACEBO Protocol outcome 1: Progression of CKD (change in eGFR) (Critical) at 6 months minimum - Actual outcome: eGFR using serum creatinine and MDRD equation at 5 years; Group 1: mean 67.6 ml/min/1.73m^2 (SD 4.9); n=37, Group 2: mean 64 ml/min/1.73m^2 (SD 6.1); n=34; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: eGFR using serum cystatin C and CKD-EPI equation at 5 years; Group 1: mean 66.4 ml/min/1.73m^2 (SD 4.9); n=37, Group 2: mean 60.8 ml/min/1.73m^2 (SD 6.3); n=34; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Alkalosis (Critical) at 6 months minimum - Actual outcome: Venous total carbon dioxide (mM) at 5 years; Group 1: mean 26.4 mM (SD 0.6); n=37, Group 2: mean 26.1 mM (SD 0.8); n=34; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all-cause and cardiovascular) (Critical) at 6 months minimum; Cardiovascular events (including chronic heart failure) (Critical) at 6 months minimum; Progression of CKD (measured by occurrence of end stage renal disease needing RRT) (Critical) at 6 months minimum; Hypertension (measured by use of antihypertensives) (Critical) at 6 months minimum; Hospitalisation (Important) at 6 months minimum; Nutrition (measured by subjective global assessment) (Critical) at 6 months minimum; Nutrition (measured by change in BMI) (Critical) at 6 months minimum; Health related quality of life (Important) at 6 months minimum

Appendix H: Economic evidence tables

H.1 Self-management

Table 152: [HOPKINS2011]

Hopkins RB, Garg A, X, Levin A, Molzahn A, Rigatto C, Singer J et al. Cost-effectiveness analysis of a randomized trial comparing care models for chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2011; 6(6):1248-1257. (Guideline Ref ID HOPKINS2011)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Cost Effectiveness analysis of RCT **Approach to analysis:** The analysis used the CanPREVENT randomised trial of 474 patients to analyse the effectiveness of models of care for the treatment of CKD. **Perspective:** Canadian healthcare system (societal perspective costs used in SA) **Time horizon:** 2 years	**Population:** Patients with stage 3-4 CKD selected on laboratory case finding method from five different primary care centres across Canada. **Intervention 1:** Multifaceted Nephrologist/Specialist Nurse supported care that targeted factors associated with the development of kidney and cardiovascular disease The intervention involves tailored care in discussion with the patient and specialist to identify risk	**Total costs (mean per patient):** Intvn 1: £2,545 Intvn 2: £3,155 Incremental (1-2): - £610 **Currency & cost year:** 2009 Canadian dollars (presented above as 2012 UK pounds‡) **Cost components incorporated:** Emergency Hospitalization Family physician Nephrology Cardiology	**QALYs (mean per patient):** Intvn 1: 1.502 Intvn 2: 1.456 Incremental (1-2): 0.046	**Intvn 1 vs.Intvn 2:** The Intervention was Dominant over the usual care comparator probability that the intervention was cost effective at £20,000 per QALY = 95% **Analysis of uncertainty:** The analysis looked at all-cause costs, which added on productivity costs for a societal perspective. The result of this was that the "dominance is even stronger" The baseline eGFR was also used to see if this had an effect. However the dominance was maintained throughout.

Treatment effect duration: 2 years **Discounting:** No	factors for disease progression and helps to manage them **Intervention 2:** Usual Care involving an explanation of kidney status after entering the study. Nephrologist only provided on call or emergency care in the case of ESRD.	Endocrinology Internist Surgeon Other physician Clinic Tests and procedures Other health care provider Study nurse Study nephrologists		
Data sources				
Health outcomes: The effectiveness was taken from a Randomized Control Trial called the CanPREVENT study[60]. Baseline event rate taken from the control arm of the trial. **Quality-of-life weights:** The utility data used was from the HUI-3 questionnaire. **Cost sources:** All events were recorded and costed by using estimates from the Ontario schedule of benefits for healthcare workers and using estimates from a case costing centre in Ontario for the unit costs of other interventions.				
Comments				
Source of funding: *supported by a New Engineering Team grant co-funded by the Canadian institutes for health research, the kidney foundation of Canada, the heart and stroke foundation of Canada and the Canadian diabetes association and by unrestricted grants from Amgen Canada, Ortho biotech and Merck Frosst Canada.* ***Limitations:*** *In guideline review of clinical effectiveness, it was noted that the trial was unblended and the randomisation method was unclear.*				
Overall applicability*: Partially Applicable. Overall quality: Potentially serious limitations**				

Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life year ‡ Converted using 2011 purchasing power parities[513]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.2 Blood pressure – combined renin-angiotensin-aldosterone system antagonists

H.2.1 Studies from 2008 guideline

Table 153: Hendry et al. 1997[262]

Modelling and costing the consequences of using an ACE inhibitor to slow the progression of renal failure in type I diabetic patients. QJM 1997 Apr; 90(4):277-282				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = Life years saved) **Study design:** Economic model **Approach to analysis:** Simulated patient transition from development of ESRF to death. **Perspective:** NHS UK **Time horizon:** 4 years **Treatment effect duration:** 4 years **Discounting:** Costs = 6% ; Outcomes = 6%	**Population:** Adult patients with insulin-dependent diabetes mellitus (IDDM) starting before the age of 30, with a history of at least 7 years and had diabetic retinopathy. **Cohort settings:** Age range = 18 to 49 M = NR **Intervention 1:** (25 mg, 3 times a day) Captopril alternative (antihypertensive medication with ACE inhibitor therapy) **Intervention 2:** Placebo alternative (antihypertensive medication	**Total costs (mean per patient over 4 years):** Intvn 1: £8,334.5 Intvn 2: £9,287.3 Incremental(2-1): The total discounted cost saving per patient over 4 years was estimated to be £953. (CI NR; p = NR) **Currency & cost year:** UK pounds. Year NR. **Cost components incorporated:**NR	**Life years saved (mean per patient):** Intvn 1: Life years saved over 4 years for a cohort of 1000 patients treated with an ACE inhibitor was estimated to be 195. Intvn 2: NR Incremental (2-1): (CI NR; p = NR)	**ICER (Intvn 2 vs.Intvn 1):** ICER was not calculated for the baseline since the intervention was shown to be the dominant strategy. SA on worst case scenario in sensitivity analysis i.e. if a risk reduction of only 18% is assumed (compared with the trial result of 50%). Here, the cost of Captopirl is £71,000 over 4 years and 52 life-years are saved; the cost per life-year saved is £1360. **Analysis of uncertainty:** One-way and multi-way sensitivity analyses were carried out on the rates of progression to ESRF and death, rate of risk reduction and the difference in the cost of care for diabetic care alone compared with the costs of treating ESRF. The results are robust to these.

	without an ACE inhibitor)			
Data sources				
Health outcomes: This study used the results from the published The Diabetic Nephropathy Collaborative Study Group, DNCSG (Lewis et al., 1993) where DNCSG is a randomized, double-blinded controlled trial.. **Quality-of-life weights:** N.A. **Cost sources:** Only direct costs were included. NHS perspective was taken. Costs of procedures and other hospital treatments were obtained from a variety of hospitals in England. Drug costs were derived from published NHS sources, ACE inhibitor treatment being costed on the basis of 25 mg captopril three times daily, giving an annual cost of £249. Costs for GP care and cardiology treatments and procedures included in the model were taken from 'Costing of Cardiology Services' [Piercy J, 1995].				
Comments				
Source of funding: Bristol-Myers Squibb Pharmaceuticals **Limitations:** Costs and benefits discounted at 6%, health effects not expressed in QALYs, study funded by manufacturer of study drug **Other:**				
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations				

Abbreviations: ACE=angiotensen-converting-enzyme; CEA = cost-effectiveness analysis; CI = 95% confidence interval; ESRF= end stage renal failure; ICER = incremental cost-effectiveness ratio; IDDM=insulin dependent diabetes mellitus; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 154 Hogan et al. 2002[274]

Hogan TJ, Elliott WJ, Seto AH, Bakris GL. Antihypertensive treatment with and without benazepril in patients with chronic renal insufficiency: a US economic evaluation. Pharmacoeconomics 2002; 20(1):37-47				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Decision analytic Markov model. **Approach to analysis:** Health states include	**Population:** Adult patients who experienced chronic renal insufficiency. **Cohort settings:** Mean age = 51 M = 73%	**Total costs $US 1999 (£UK 1999), mean per patient over 7 years:** Intvn 1: 88,715 (£57,899) Intvn 2: 101,706 (£66,378) Incremental(2-1): 12,991 (£8,479)	**QALYs (mean per patient over 7 years):** Intvn 1: 4.989 Intvn 2: 4.897 Incremental (2-1): -0.092 (CI NR; p = NR)	**ICER (Intvn 2 vs.Intvn 1):** Benazepril was less expensive and more effective than placebo. That is, intervention 1 dominated intervention 2 over a 7 year period. CI: NR Probability Intvn 2 cost-effective (£20K/30K threshold): NR

chronic renal impairment, dialysis, transplant and death. **Perspective:** US Healthcare payer. **Time horizon:** 7 years **Treatment effect duration:** **Discounting:** Costs = 3% ; Outcomes = 3%	**Intervention 1:** Antihypertensive treatment with benazepril. Dose and quantity NR. **Intervention 2:** Placebo	(CI NR; p = NR) **Currency & cost year:** 1999 $US‡ **Cost components incorporated:** Medical treatment, dialysis, renal transplantation, post-transplant maintenance.		**Analysis of uncertainty:** Results favouring the benazepril therapy arm were found in sensitivity analyses of changes in key model parameters.
Data sources				
Health outcomes: The effectiveness data were extracted from a randomised controlled trial (the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study) and its extension study (Locatelli F et al., 1997). **Quality-of-life weights:** Health utilities employed in the model were determined by analytical estimate based on reference to the quality-of-life literature. **Cost sources:** Estimated medical treatment costs were obtained from various public sources. Direct medical costs were aggregated and included the costs of all appropriate healthcare resources consumed in the care and treatment of the health state to which these costs are assigned. Costs of dialysis, renal transplantation ans post-transplant maintenance care were obtained from the United States Renal Data System (USRDS) of the National Institutes of Health. Estimates of direct medical costs in the 6 months preceding death were derived from the Healthcare Financing Administration.				
Comments				
Source of funding: Supported in part by Novartis Pharmaceuticals. **Limitations:** USA setting. Study funded by Novartis the manufacturer of benazepril. **Other:**				
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations.				

Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

‡ Converted using 1999 purchasing power parities[513]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 155: Palmer et al. 2004[516]

Palmer AJ, Annemans L, Roze S, Lamotte M, Rodby RA, Bilous RW. An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. *Journal of Human Hypertension* 2004; 18:733-738.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CEA (health outcome = life-years saved) **Study design:** Markov decision analytic model. **Approach to analysis:** Simulation of progression from DSC, ESRD (dialysis or transplant) or death. **Perspective:** . UK NHS **Time horizon:** 10 years **Discounting:** Costs = 6%; Outcomes = 1.5%.	**Population:** Patients with type 2 diabetes, hypertension and nephropathy. **Cohort settings:** Start age = 59 M = NR **Intervention 1:** Irbesartan 300mg/d **Intervention 2:** Amlodopine 10mg/d **Intervention 3:** Standard antihypertensive. (conventional medications excluding. ACE inhibitors, ARBs, and dihydropyridien CCBs)	**Total costs at 10 years £ (mean per patient):** Intvn 1: 20,884 Intvn 2: 27,417 Intvn 3: 24,642 Incremental (2-1): (CI NR; p = NR) **Currency & cost year:** UK£s. Published cost data from 1998 to 2003. **Cost components incorporated: drug costs,** Costs of medications and ESRD were assessed for patients in all three treatment arms.	**Increase in life expectancy at 10 years (mean years per patient):** Intvn 1:NR Intvn 2:NR Intvn 3:NR Incremental (2-1):- 0.08 Incremental (3-1):-0.23 (CI NR; p = NR)	**ICER (Intvn 2 vs.Intvn 1):** ICER not calculated as irbesartan dominates amlodopine and standard antihypertensive. CI:NR Probability Intvn 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** One-way sensitivity analysis showed that the annual costs of dialysis in the UK would have to fall below £3,000 irbesartan would no longer be cost saving compared to standard antihypertensives alone.
Data sources				
Health outcomes: The effectiveness data was derived from the Irbesartan in Diabetic Nephropathy Trial (IDNT)[384] and UK-specific ESRD management and outcomes data, which were from the UK Renal Registry Report and a previous study review. **Quality-of-life weights:**N.A. **Cost sources:** The cost of each dose was calculated from the British National Formulary. RRT costs were taken from published UK-specific sources. Cost data were derived from papers published between 1998 and 2003.				
Comments				
Source of funding: Sponsored by an unrestricted grant from Bristol-Myers Squibb. **Limitations:** Costs discounted at 5%, benefits at 1.5%. Health effects not expressed as QALYs. One way sensitivity only. Study sponsored by study drug manufacturer. **Other:**				

Overall applicability*: Partially applicable	**Overall quality**:** Minor limitations

*Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin 2 receptor blockers; CCB = calcium channel blockers; CEA = cost-effectiveness analysis; CI = 95% confidence interval; DSC = doubling of serum creatinine; ESRD = end stage renal disease; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years; RRT=renal replacement therapy; * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 156: Palmer et al. 2007[518]

Palmer AJ, Valentine WJ, Ray JA. Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economic analysis. International Journal of Clinical Practice, 2007: 61(10):1626-33.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = life-years saved) **Study design:** Markov decision analytic model. **Approach to analysis:** Simulation of progression to DSC, overt nephropathy, ESRD (dialysis or transplant) or death. **Perspective:** UK NHS **Time horizon:** 25 years **Discounting:** Costs = 3.5%; Outcomes = 3.5%.	**Population:** Patients with type 2 diabetes, hypertension and microalbuminuria. **Cohort settings:** Start age = NR M = NR **Intervention 1:** Early (24-hr UAE 20-199µg/min) irbesartan 300mg/d **Intervention 2:** Late (UAE 1100mg/24hr) irbesartan 300mg/d **Intervention 3:** Standard antihypertensive.	**Total costs £ (mean per patient):** Intvn 1: 6,735 Intvn 2: 9,045 Intvn 3: 10,536 Incremental (1-3): -3801 ±327 Incremental (1-2):-2310±327 **Currency & cost year:** 2002 UK£ **Cost components incorporated: drug costs,** Medications and renal replacement therapy.	**ESRD** Intvn 1: 7.2% Intvn 2: 15.9% Intvn 3: 19.6% **Life expectancy (mean years per patient):** Intvn 1:11.00 Intvn 2:10.20 Intvn 3:10.18 Incremental (1-3): 0.83 ±0.04 Incremental (1-2):0.81±0.04	Early irbesartan dominates **Analysis of uncertainty:** This was performed using the confidence limits for the progression rates and varying the mortality rates. Early irbesartan was dominant in all analyses.NR

	(conventional medications excluding ACE inhibitors, ARBs, and dihydropyridien CCBs)			

Data sources
Health outcomes: The effectiveness data was derived from the Irbesartan in Diabetic Nephropathy Trial (IDNT)[384] and IRMA-2 trial[527] UK-specific ESRD management and data were from the UK Renal Registry Report. **Quality-of-life weights:** NA. **Cost sources:** Renal replacement therapy costs were taken from published UK-specific sources. Cost data were derived from papers published between 1998 and 2003.
Comments
Source of funding: Bristol-Myers Squibb and Sanofi-Aventis. **Limitations:** Health effects not expressed as QALYs. One way sensitivity only. Study sponsored by study drug manufacturer.
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations

*Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin 2 receptor blockers; CCB = calcium channel blockers; CEA = cost-effectiveness analysis; CI = 95% confidence interval; DSC = doubling of serum creatinine; ESRD = end stage renal disease; NA=Not applicable; NR = not reported; * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 157: Ruggenenti et al. 2001[592]

Ruggenenti P, Pagano E, Tammuzzo L, Benini R, Garattini L, Remuzzi G. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. Kidney International 2001 Jan; 59(1):286-294				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = progression to ESRD and life expectancy.)	**Population:** Patients with non-diabetic chronic nephropathies. **Cohort settings:** Mean age from trial data =	**Total costs $US (mean per patient): GFR decline model** Intvn 1:84,900 (53,215) Intvn 2:101,505 (63,623) Incremental (2-1):	**Overall survival (mean years per patient): GFR decline model** Intvn 1:11.6±1.2 Intvn 2:10.4±1.1	Results from both models showed Intervention 1 to be less expensive and more effective than Intervention 2. CI:NR Probability Intvn 2 cost-effective (£20K/30K

Study design: Decision analytic Marcov model. **Approach to analysis:** Two models: one based on assumption re GFR rate of decline and one events- based model. Events based model (health outcome = incidence of ESRD over a lifetime) **Perspective:** Italy health care payer. **Time horizon:** Lifetime **Treatment effect duration:** Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	46 and 50 for ramipril and placebo groups. M = 84% and 72% **Intervention 1:** Ramipril **Intervention 2:** Placebo. Dose and duration not reported. Both treatment groups received conventional antihypertensive therapy (calcium channel blockers, diuretics, alpha blockers, beta blockers and /or centrally acting agents).	16,605(10,408) **Total costs $US (mean per patient): events based model** Intvn 1:81,849 (51,303) Intvn 2:105,723 (66,267) Incremental (2-1): 23,874 (14,964) Cost year : Assumed as year of publication , 2001 presented here as 2001 UK £‡. **Cost components incorporated:** Direct medical costs: out-patient and in-patient care, medications, medical equipment, supplies and laboratory tests. Patient management costs before progression to ESRD were extrapolated from the direct costs of patients on ramipril or placebo plus conventional therapy during the REIN trial.	Incremental (2-1):-1.2 (CI NR) **Overall survival (mean years per patient): events based model** Intvn 1:10.3±0.9 Intvn 2:8.9±0.8 Incremental (2-1):-1.4 (CI NR)	threshold):NR **Analysis of uncertainty:** A sensitivity analysis was done to compute the best case and worst case results for costs, mortality rate, and discount rate. Results were robust to these.
Data sources				
Health outcomes: The effectiveness data were derived from the Ramipril Efficacy in Nephropathy Trial (REIN). **Quality-of-life weights:** N.A. **Cost sources:** Public prices were				

considered to calculate the expense of medications. The costs of dialysis and renal transplantation were estimated on the basis of previously published data. Price year was not stated though costs were collected from studies published between 1990 and 1997.	
Comments:	
Source of funding: Aventis Pharma AG. **Limitations:** Italy setting costed in US dollars. Study is funded by drug manufacturer. Did not estimate QALYs. Did not report cost year used. **Other:**	
Overall applicability*: Partially applicable	**Overall quality**:** Minor limitations

Abbreviations: CEA = cost-effectiveness analysis; CI = 95% confidence interval; ESRD = end stage renal disease; GFR=glomerular filtration rate; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; ǂ Converted using 2001 purchasing power parities[513]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 158: Schadlich et. al. 2001[611]

Schadlich PK, Brecht JG, Brunetti M, Pagano E, Rangoonwala B, Huppertz E. Cost effectiveness of ramipril in patients with non-diabetic nephropathy and hypertension: economic evaluation of Ramipril Efficacy in Nephropathy (REIN) Study for Germany from the perspective of statutory health insurance. Pharmacoeconomics 2001; 19(5: Pt 1): t-512.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = The number of patient years of chronic long-term dialysis avoided (PYCDA)) **Study design:** Economic model **Approach to analysis:** Secondary analysis of	**Population:** Patients with non-diabetic nephropathy and hypertension.. **Cohort settings:** Start age = 49 M = 85% **Intervention 1:** Ramipril (target =5mg/day) **Intervention 2:**	**Total costs over 3 years in German DM (£UK) , mean per patient:** Intvn 1:NR Intvn 2:NR Incremental (2-1):173,917 (57,442) (CI NR; p = NR) **Currency & cost year:** German deutchmarks 1996	**Patient-year of chronic dialysis avoided (PYCDA) over 3 years (mean per patient):** Intvn 1:NR Intvn 2:NR Incremental (2-1): -0.212 (CI NR; p = NR)	**ICER (Intvn 2 vs.Intvn 1):** Ramipril dominated placebo. Was more effective and less expensive over 3 year period. CI: Probability Intvn 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Deterministic analysis (da) showed the cost for chronic dialysis per patient per year had by far the greatest impact on costs savings associated with ramipril. Probabilistic analysis (pa) showed that in 95% of simulations ramipril

published data. **Perspective:** Germany Statutory Health Insurance provider **Time horizon:** Three years. **Discounting:** Costs = 5%; Outcomes = 5%.	Placebo	(presented also as 1996 UK pounds‡) **Cost components incorporated:** Ramipril (priced in 1999 DM), Chronic dialysis: dialytic procedures, medical services, erythroporitin usage, treatment of complications induced by dialysis, treatment of comorbidity and transportation.		strategy was less expensive than placebo.
Data sources				
Health outcomes: The effectiveness data were mainly derived from the Ramipril Efficacy in Nephropathy Trial (REIN). Other probability estimates were obtained from a review of published literature. **Quality-of-life weights:** N.A. **Cost sources:** An average cost for ramipril was derived from the interval-related distribution of daily doses of 1.25, 2.5 and 5mg, respectively. The frequency of the different procedures was taken from the Health Report for Germany edited by the Federal Statistical Office and from expert knowledge. The average costs for chronic dialysis per patient per year were given by the weighted mean of SHI expenses for each dialysis procedure.				
Comments				
Source of funding: Aventis Pharma Deutschland GmbH, D-65812 Bad Soden/Taunus, Germany. **Limitations:** Setting Germany, priced in DM, did not express health effects in QALYs. Discounted costs and benefits at 5%. Time horizon = 3 years only. Study funded by manufacturer of study drug. **Other:**				
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations				

Abbreviations: CEA = cost-effectiveness analysis; CI = 95% confidence interval; da = deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; PYCDA= patient-year of chronic dialysis avoided; QALYs = quality-adjusted life years

‡ Converted using 1996 purchasing power parities[513]

** Directly applicable / Partialliy applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 159: van Hout et al. 1997 [695]

van Hout BA, Simeon GP, McDonnell J, Mann JF. Economic evaluation of benazepril in chronic renal insufficiency. Kidney International - Supplement 1997 Dec; 63:S159-62, 1997 Dec.:S159-S162.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = life years) **Study design:** Markov chain model **Approach to analysis:** Health states: CRI, HD, post-transplant, second HD, Death. **Perspective:** Not stated. Setting = Netherlands, Switzerland, Germany. **Time horizon:** 10 years **Discounting:** Costs = 5% ; Outcomes = 5%	**Population:** adults with chronic renal insufficiency. **Cohort settings:** Start age = 55 M = 100% **Intervention 1:** Benazepril Dose and duration NR. **Intervention 2:** Placebo	**Total costs in $US (£UK) at 10 years (mean per patient):** Intvn 1:39,445 (25,321) Intvn 2:67,459 (43,304) Incremental (2-1): 28,014 (17,983) (CI NR; p = NR) **Currency & cost year:** 1996 US dollars presented here as 1996 UK pounds‡) **Cost components incorporated:** Being in each phase of the renal disease progression process: transplantation, irreversible graft rejection and dying.	**Life years at 10 years (mean per patient):** Intvn 1:7.59 Intvn 2:7.28 Incremental (2-1): -0.32 (CI NR; p = NR) **% surviving without ESRD at 10 years :** Intvn 1:74.32 Intvn 2:56.18 Incremental (2-1):- 18.14	**ICER (Intvn 2 vs.Intvn 1):** ICER was not calculated since the benazepril intervention was shown to be the dominant strategy CI: Probability Intvn 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Univariate sensitivity analysis was performed on the costs of end-stage renal disease, the costs of the preventive therapy and other important parameters used in the model. The results indicate that the conclusion of a combination of additional effectiveness and cost savings is extremely robust.
Data sources				
Health outcomes: The effectiveness data were extracted from a randomised controlled trial (the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study). The survival probabilities and some other transition probabilities were estimated using the data from a Dutch foundation (RENINE) responsible for the registration of all ESRD patients in the Netherlands. **Quality-of-life weights:** N.A. **Cost sources:** Estimates of costs of ESRD were primarily based upon two earlier studies addressing the cost effectiveness of the ESRD program in the Netherlands and adjusted to the current situation by consulting a panel of experts.				

Comments
Source of funding: NR. **Limitations:** Setting is Netherlands, Switzerland and Germany. Prices in $US. Value of health effects not expressed in QALYs. Perspective unclear. **Other:** Note again that perspective of the study was not given and resource utilisation and cost data were not reported separately so this may limit to applicability of generalisability of results to other settings, in particular the NHS. There also seems to be a slight lack of information provided in this study e.g. the sensitivity analysis.
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations.

Abbreviations: CEA = cost-effectiveness analysis; CI = 95% confidence interval; CRI= chronic renal insufficiency; HD = haemodialysis; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years

‡ Converted using 1996 purchasing power parities[513]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 160: Vora et al. 2005[703]

Vora J, Carides G, Robinson P. Effects of Losartan-based therapy on the incidence of end-stage renal disease and associated costs in type 2 diabetes mellitus: A retrospective cost-effectiveness analysis in the United Kingdom. Current Therapeutic Research, Clinical & Experimental 2005;66(6):475-485				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = life years saved) **Study design:** economic evaluation based on trial data. **Approach to analysis:** Survival and costs projected over lifetime. **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs =	**Population:** Patients with nephropathy from Type II diabetes. **Cohort settings:** Start age = NR M = NR **Intervention 1:** Losartan **Intervention 2:** Conventional antihypertensive treatment: calcium channel blockers; diuretics; alpha blockers; beta blockers; centrally	**Total costs £UK (mean per patient):** Intvn 1:14,777 Intvn 2: 21,399 Incremental (2-1): 6,622 (CI: 2,653 to 10,591; p = 0.001) **Currency & cost year:** 2004 £UK **Cost components incorporated:** Losartan (£768 over lifetime),	**Life years saved (mean per patient):** Intvn 1: 7.82 Intvn 2: 7.38 Incremental (2-1): -0.44 (CI -0.16 to -0.71; p = 0.002)	**ICER (Intvn 2 vs.Intvn 1):** Intervention 1 dominated intervention 2. Probability Intvn 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Base Case results were robust to SA on costs, LYs saved, and when cost of renal replacement therapy was reduced by 50%.

3.5% ;Outcomes =3.5%	acting agents.	haemodialysis and peritoneal dialysis (£17,657 to £23,864 annually).		

Data sources
Health outcomes: The effectiveness evidence was derived from the Reduction of Endpoints in NIDDM (noninsulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (REENAL) study which a prospective, randomised, double-blind, placebo-controlled clinical trial [Brenner 2001]. **Quality-of-life weights:** N.A. **Cost sources:** Cost of losartan estimated from the unit cost of losartan to the UK NHS multiplied by average usage during the RENAAL study. Annual costs of haemodialysis and peritoneal dialysis were derived from the UK Transplant website, where costs relevant to the NHS were considered. In a secondary analysis, the costs of haemodialysis and peritoneal dialysis were taken from the UK 2-Center European Dialysis and Cost-Effectiveness (EURODICE) study.
Comments
Source of funding: NR. First author has received grants from Merck Sharp & Dohme, and other authors may hold stock in same company. **Limitations:** Health outcomes not expressed as QALYs. Funding source not reported. However, authors may hold stock in company that manufactures study drug. **Other:**
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations

Abbreviations: CEA = cost-effectiveness analysis; CI = 95% confidence interval; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.2.2 New studies from 2014 update

Table 161 Adarkwah et al. 2013[12]

Adarkwah CC, Gandjour A, Akkerman M, Evers S. To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research. Netherlands 2013; 37(2-3):168-180. (Guideline Ref ID ADARKWAH2013)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY)	**Population:** Non diabetic proteinuric patients with advanced renal	**Total costs (mean per patient):** Intervention 1: £171,720	**QALYs (mean per patient):** Intervention 1: 9.32 Intervention 2: 11.11	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates Intervention 1.

Study design: **Approach to analysis:** Markov Decision Model- health states included: Advanced Renal Disease, ESRD, and Death. **Perspective:** Netherlands health care system perspective **Time horizon/Follow-up:** lifetime (until 100 years of age) **Discounting:** Costs: 4%; Outcomes: 1.5%	disease (n = 1000) **Cohort settings:** Start age: 44 **Intervention 1:** Placebo **Intervention 2:** ACE inhibitor- Benezapril 10 mg twice a day. All patients received other antihypertensive agents (diuretics, alpha- or beta-blockers, calcium –channel antagonists, or some combination of these medications). No other Renin Angiotensin Antagonist System inhibitors given.	Intervention 2: £142,647 Incremental (2−1): -£29,073 (CI NR; p = NR) **Currency & cost year:** 2010 Euros presented above as 2010 UK pounds[(a)] Intvn 1: € 220,942 Intvn 2: € 183,535 **Cost components incorporated:** General health care expenditure not related to CKD; ACE inhibitor (20mg benazepril daily; 5mg Enalapril daily in the SA); ESRD – including transplantation, dialysis, home/in-centre hemodialysis, CAPD, CCPD	Incremental (2−1): 1.79 (CI NR; p = NR)	**Analysis of uncertainty:** Univariate DA varied parameter values to their at 95% confidence interval limits. Sensitivity Analysis were conducted on the annual transition probabilities from advanced renal insufficiency to ESRD; effectiveness of ACE inhibitor; utilities; costs; standard mortality rate; discount rate (0%-10%). Base case results remained robust.
Data sources				

Health outcomes: Transition probabilities on progression from advanced renal insufficiency taken from Ihle BU, Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ: Angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992; 11:234-242. & Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW: Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006; 354; 131-140. Transitions probabilities without ESRD to mortality were regarded as a function of age specific mortality rates. Transition probabilities with ESRD to mortality was calculated as the age specific mortality rate multiplied by the standard mortality ratio for patients with advanced renal disease (taken from Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M; Alberta Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010; 303:424-429. **Quality-of-life weights:** utility losses were calculated according to the relevant health state and an age dependent loss of utility. Health State preference weights were derived from patients using a Time-Trade-Off approach.[(d)] **Cost sources:** Resource consumption based on K/DOQI and NICE CG73. Costs of drugs based on Dutch Health Authority 2010 Report and included 6% value-based tax as well as 3 monthly pharmacists' prescription fee. Annual costs of ESRD based on prevalence of different types of dialysis & transplantation (Dutch National Register2011) and de Wit et al 1998 [(e)]. Post-transplant costs (first and subsequent years) based on German costs from Nebel 2002 [(f)].

Comments

Source of funding: NR **Limitations:** Exclusion of cardiovascular events in model such that results of analysis are conservative; The study from which effectiveness data was derived (Hou et al 2006) was conducted in China- the efficacy of ACE inhibitors may differ in white Caucasian populations.

Overall applicability[(b)]: Partially Applicable **Overall quality[(c)]:** Minor Limitations

Abbreviations: CI: 95% confidence interval; CUA: cost–utility analysis; DA: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 means worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years.

(a) Converted using 2012 purchasing power parities [512]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

(d) Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P, Pavkov ME, Jordan R, Hailpern SM, Schoolwerth AC, Williams DE; Centers for Disease Control and Prevention CKD Initiative: A health policy model of CKD: 2. The cost-effectiveness of microabluminuria screening. AM J Kidney Dis 2010; 55:463-473. ; Churchill DN, Torrance GW, Taylor DW, Barnes CC, Ludwin D, Shmizu A, and Smith EK: Measurement of quality of life in end-stage renal diseases: the time trade-off approach. Clin Invest med 1987; 10:14-20. Arnesen T, Trommald M: Roughly right or precisely wrong? Systematic review of quality of life weights elicited with the time trade-off method. J Health Serv Res Policy 2004; 9:43-50.

(e) De Wit GA, Ramsteijn PG, de Charro FT: Economic evaluation of end stage renal disease treatment. Health Policy 1998; 44:215-232.

(f) Nebel M: Costs of renal replacement therapies in Germany in 1999. Nieren-und Hochdruckkrankheiten 2002; 3: 85-92.

Table 162: Delea et al. 2009A[160]

Delea TE, Sofrygin O, Palmer JL, Lau H, Munk VC, Sung J, Charney A, Parving H-H, Sullivan SD. Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. *Journal of the American Society of Nephrology.* 2009; 20(10):2205-2213. *(Guideline Ref ID DELEA2009A)*				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Markov model (health states: microalbuminuria, early overt nephropathy, advanced overt nephropathy , doubling of serum creatinine, ESRD dialysis, ESRD transplant, dead) 6 month cycles **Perspective:** US payer perspective **Time horizon:** 20 yrs approximate lifetime projection	**Population:** Patients with type 2 diabetes, hypertension, and renal disease from the AVOID trial **Cohort settings:** Start age = 61 M = 71% **Intervention 1:** Losartan 100 mg/d and optimal antihypertensive therapy (losartan only) **Intervention 2:** Aliskerin 300 mg/d plus losartan 100 mg/d and optimal antihypertensive treatment (aliskiren plus losartan)	**Discounted Total Costs (mean per patient):** Intvn 1: £39 517 Intvn 2: £41 404 Incremental (2-1): £1888 **Currency & cost year:** Assumed 2008 US dollars (presented here as 2008 UK pounds‡) **Cost components incorporated:** Direct health care costs including the medication costs and treatment and routine care costs.	**Discounted QALYs (mean per patient):** Intvn 1: 5.8808 Intvn 2: 5.9775 Incremental (2-1):0.0967	**ICER (Intvn 2 vs.Intvn 1):** £19 500 per QALY gained (pa) Probability Intvn 1 cost-effective (£32K threshold): 60% **Analysis of uncertainty:** Deterministic SA performed on transition probabilities, costs, disutilities, time frame, starting age and annual discount rate for costs and QALYs. Intervention 2 was not cost effective if relative risk reduction of progression from early overt nephropathy to advanced overt nephropathy is low, if the cost of aliskiren is over £913, if the time frame is 10 years, and if the treatment starting age is 70. Baseline results robust to changes in all other parameters. In the probabilistic analysis, the cost effectiveness of aliskiren ranged from dominated to dominant, reflecting

Discounting: Costs =3%; Outcomes =3%	Note: Both treatments given until death, dialysis, or renal transplantation.			uncertainty around the probabilities of progression of renal disease derived from AVOID

Data sources

Health outcomes: Transition Probabilities for Microalbuminuria, early overt nephropathy, and advanced overt nephropathy for the first 6 months were estimated by fitting multinomial logit models to data from the AVOID trial. For following months, transitions were estimated using Bayesian conjugate analyses of these data. Probabilities for advanced overt nephrology to doubling of serum creatinine and End-Stage-Renal-Disease from PRIME model. Probability of transplantation from US Renal Data system. Probabilities of death for patients without ESRD from US data in WHO life tables and the PRIME model. Mortality for patients with ESRD was estimated using data from the US Renal Data System. **Quality-of-life weights:** Utilities were calculated by multiplying age-specific utilities for US population by disutility estimates. Disutilities for non ESRD states based on time trade-off values from Beaver Dam health outcomes study [(a)]. Disutility for dialysis and transplantation from diabetic patients Coffey et al 2002[(b)]. The disutility for renal transplantation was based on a preference study of health workers in Canada using the time trade-off values Kiberd & Jindal 1995[(c)]. **Cost sources:** Pharmacy costs based on wholesale acquisition costs and annual costs of ESRD and transplantation from the US Renal Data System. Average daily resource consumption from IMS Health National Prescribing data set 2008; Antihypertensive treatment resource use derived from AVOID trial.

Comments

Source of funding: Novartis Pharmaceuticals Corporation **Limitations:** The UK costs for renal transplant; dialysis; and routine care for T2D are likely to be less than the US costs stated here. The model does not reflect the risks and benefits seen in the later ALTITUDE study. **Other:** Note that 75% of patients began the model simulation in the overt nephropathy states.

Overall applicability*: Partially Applicable **Overall quality**:** Potentially Serious Limitations

Abbreviations: (a) = Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, Martin PA: The Beaver Dam Health outcome Study: Initial catalog of health-state quality factors. IMed Decision Making 13:89-102, 1993. AVOID = Aliskiren in the Evaluation of Proteinuria in Diabetes trial lasted 6 months ; (b) = Coffey JT, Brandle M, Zhou H, Marriot D, Burke R, Tabaei BP, Engelgau MM, Kaplin RM, Herman WH: Valuing health-related quality of life in diabetes. Diabetes Care 25: 2238-2243, 2002; (c) = Kiberd BA, Jindal KK: Screening to prevent renal failure in insulin dependent diabetic patients: An economic evaluation. BMJ 311: 1595-1599, 1995; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); IDNT = Irbesartan in Diabetic Nephropathy Trial; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years SA = Sensitivity Analysis; ‡ Converted using 2008 purchasing power parities [513]; ** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.3 Vitamin D supplements in the management of CKD-mineral and bone disorders

Table 163: NUIJTEN 2010[493]

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome = QALY) **Study design:** Markov Model **Perspective:** UK NHS **Time horizon:** 10 years **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Population:** Hypothetical cohort of CKD patients with secondary hyperparathyroidism **Intervention 1[a]:** Alfacacidol, a non-selective Vitamin D receptor (VDR) Activator **Intervention 2[a]:** Paricalcitol	**Total costs (mean per patient):** Intvn 1:£13,581 Intvn 2:£16,805 Incremental (2-1): £3,224 **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** medication, costs associated with renal failure (dialysis and transplantation); complications (cardiovascular outcomes and fractures); hospitalisations, rehabilitation and routine monitoring including preventative treatment (ACE inhibitors - ARBs).	**QALYs (mean per patient):** Intvn 1:4.342 Intvn 2:4.807 Incremental (2-1):0.465	**ICER (Intvn 2 vs.Intvn 1):** £6933 per QALY gained **Analysis of uncertainty:** SA conducted on annual probability of clinical event, risk of mortality in progression, mortality in CKD- 3, CKD-4, CKD-5, cost per hospitalisation, progression of proteinuria, progression to proteinuria, prevalence of proteinuria and progression of CKD-3 to CKD-4. Results were sensitive to prevalence of proteinuria. PSA conducted and the CEAC shows that the probability is 0.82 that the ICER of paricacitol is less than £10,000 / QALY.
Data sources				
Progression Rates between CKD stages from USA study (Keith et al 2002) with amendments to progression rate CKD 5 to transplant/dialysis (UK Palmer and Rodby				

2004); CKD 3 to CKD 4 alfacacidol (USA Bakris et al 2005 & Smith et al 2004);CKD 3 to CKD 4 Paricalcitol (USA Schumock 2008). Hospitalisation rates from (USA Smith et al 2004) and were similar for both drugs. Mortality rates -- CKD 5 for alfacacidol (UK Palmer and Rodby 2004), CKD 5 for paricalcitol (USA Teng et al 2003). Mortality rates for CKD 1-4 for both Paricalcitol and Alfacacidol (USA Keith et al 2002). Clinical event probabilities documented as the incidence of clinical event (cardiovascular event/fracture) was similar for both drugs and derived from (Kalantar Zadeh et al 2006). The annual risk of hospitalisation was similar for both drugs and was derived from (USA Dobrez et al 2004).**Quality-of-life weights:** Severe CKD (stage five; haemodialysis, peritoneal dialysis, and transplantation) values from UK estimates for patients using SF36 and EQ5D; Utilities for CKD stages 2, 3, 4 from a US population which used the time trade-off method. **Cost sources:** Medication costs from the MIMS; Dialysis, Transplant, Cardiovascular complications and fractures from published UK and international studies from years 2000-2004. Hospitalisation, rehabilitation and routine monitoring costs from published UK studies. All costs inflated to 2006 figures.

Comments

Source of funding: Abbott, manufacturer of paricalcitol **Limitations:** Treatment effects are not derived from randomised evidence and therefore there is a high risk of bias. Dosage and duration of medication was not reported.

Overall applicability*: Directly applicable **Overall quality**:** Potentially serious limitations

Abbreviations: [a] = Drug administered in oral form for CKD 3 & CKD4; intravenous formulation for CKD 5; ACE inhibitors -ARBs = Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), CKD = Chronic Kidney Disease; CUA= Cost Utility Analysis; SF36 = Short Form 36 Health Survey; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Appendix I: Forest plots

I.1 Measuring kidney function

I.1.1 Accuracy (P30)

Figure 15: P30 – MDRD vs.CKD EPI (sCr) vs.CKD EPI Cystatin C vs.CKD EPI combined equation

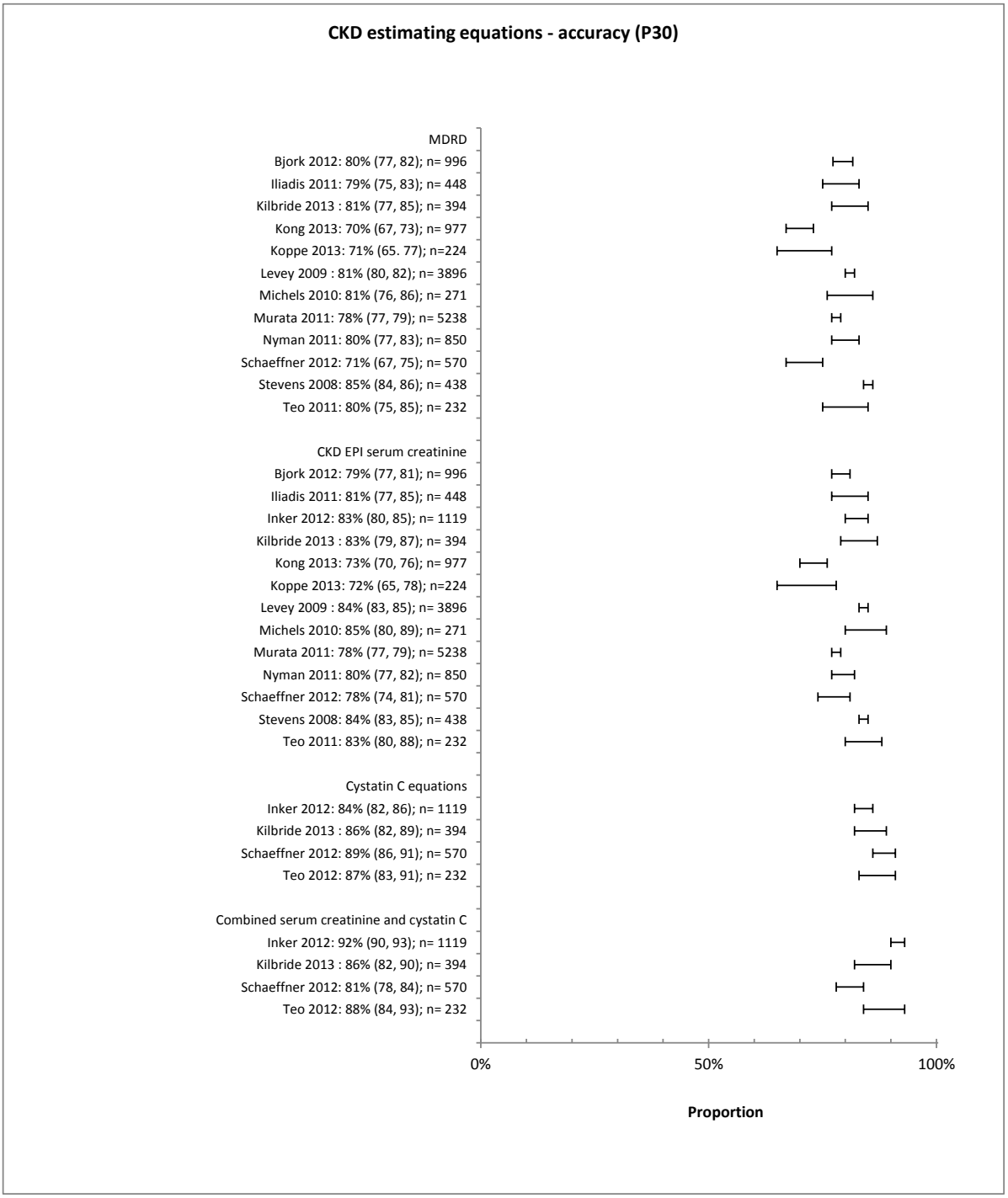


Figure 16: P30 – subgroup GFR >60 ml/min/1.73 m^2

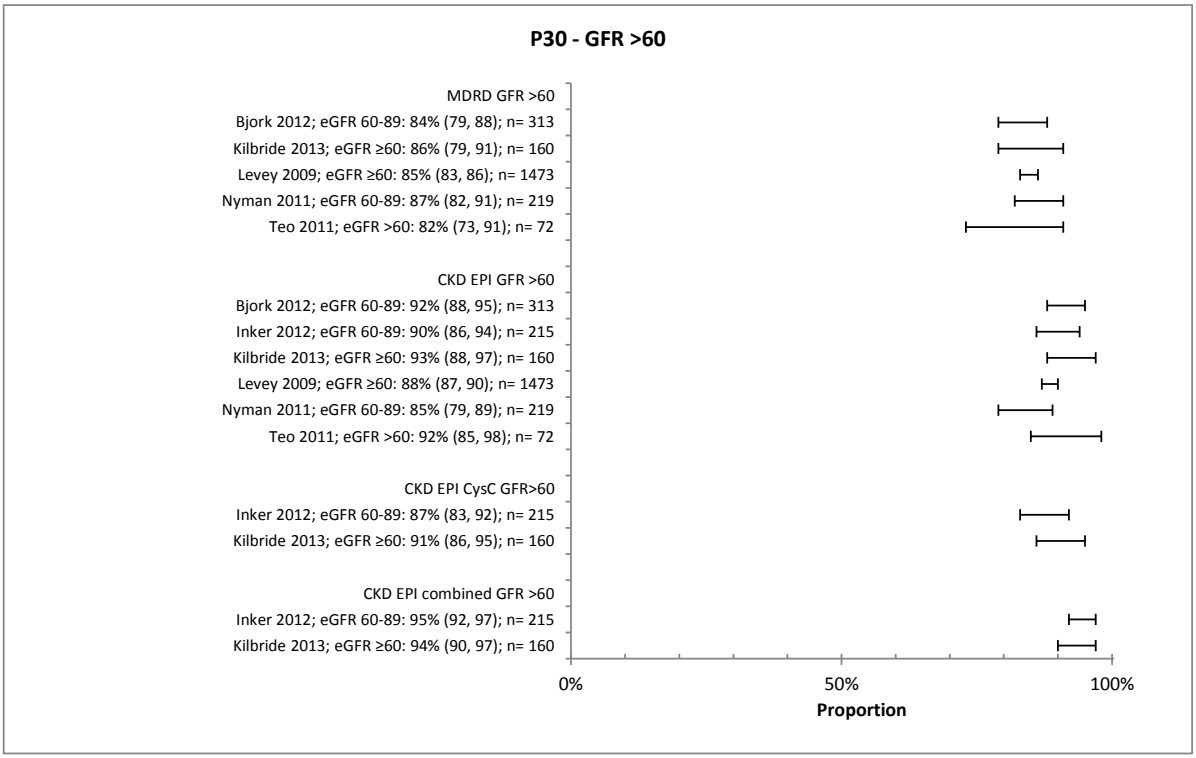


Figure 17: P30 – subgroup GFR <60 ml/min/1.73 m^2

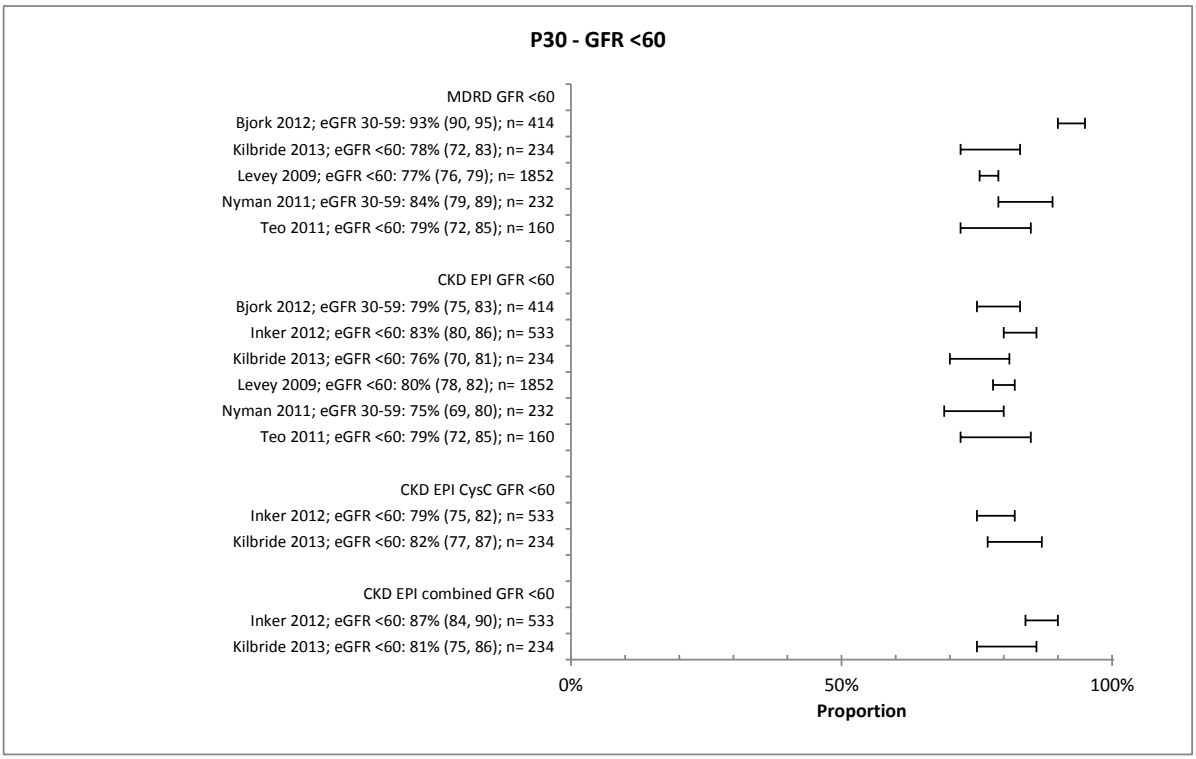
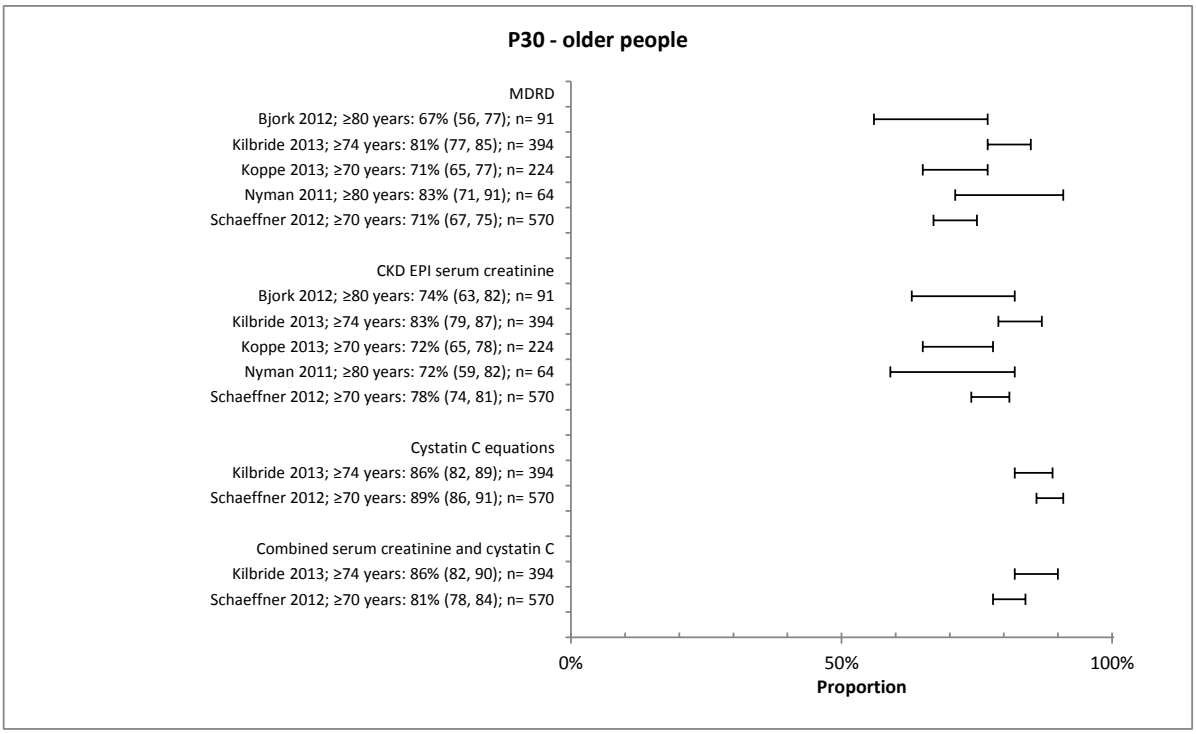
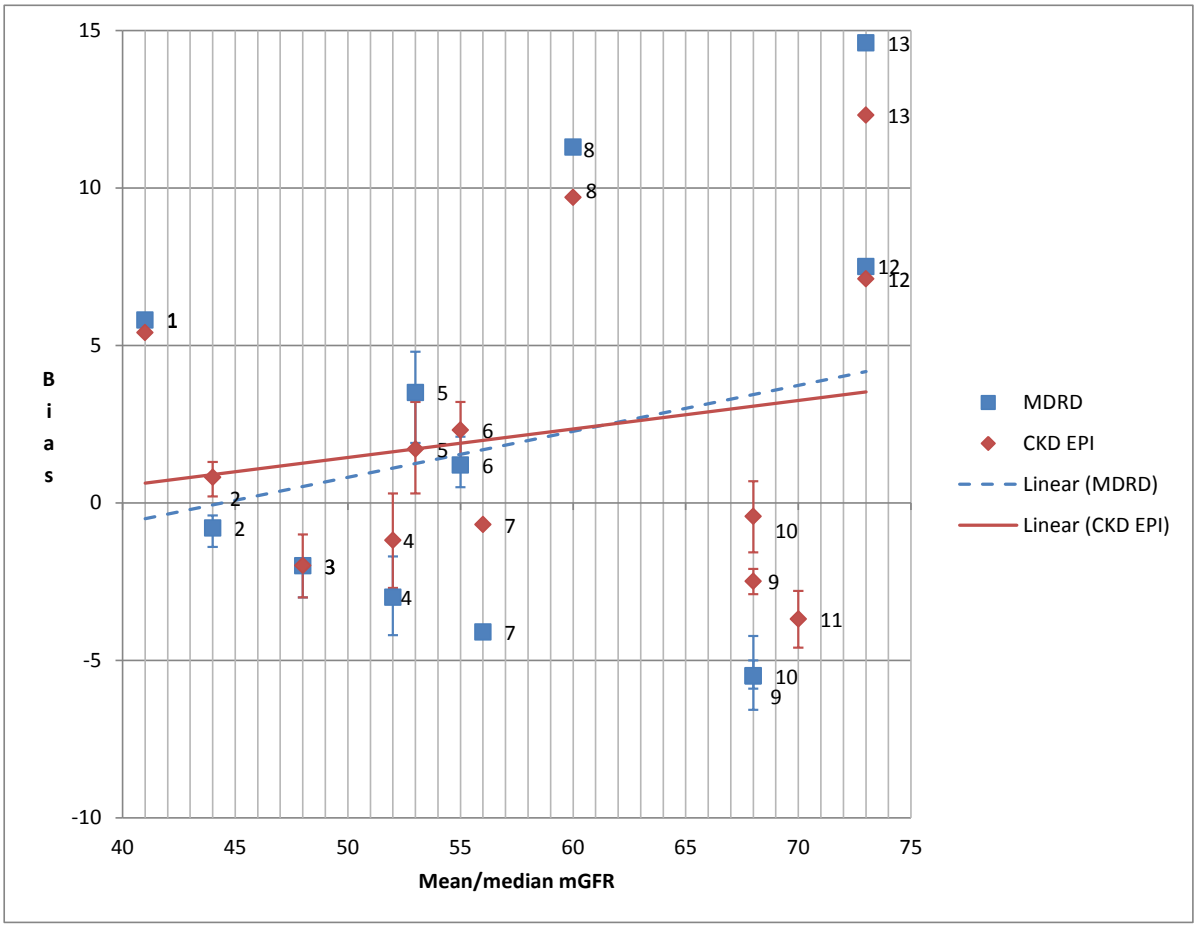


Figure 18: P30 – older people



I.1.2 Bias

Figure 19: Bias MDRD versus CKD EPI (sCr) (negative values underestimate)



Number represents study to indicate paired data. Note studies 10 and 11 report mean bias, all others report median.
1 Koppe et al 2013[352]

2 Bjork et al 2012[81]

3 Stevens et al 2008[651]

4 Teo et al 2011[669]

5 Kilbride et al 2013[341]

6 Nyman et al 2011[494]

7 Murata et al 2011[462]

8 Schaeffner et al 2012[612]

9 Levey et al 2009[379]

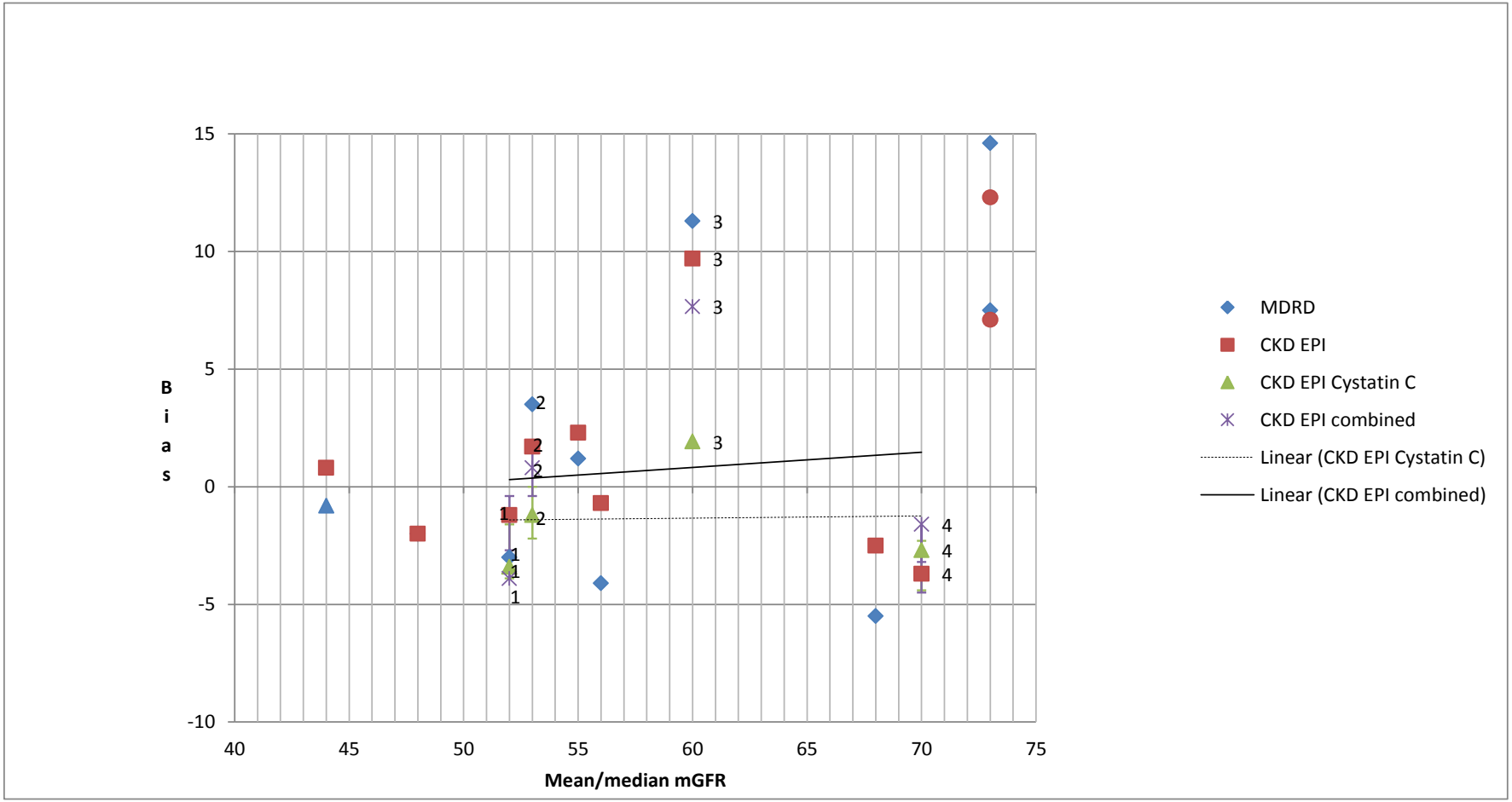
10 Kong et al 2013[350]

11 Inker et al 2012[299]

12 Iliadis et al 2011[292]

13 Michels et al 2010[451]

Figure 20: Bias – MDRD versus CKD EPI (sCr) versus CKD EPI (CysC) versus CKD EPI (combined)

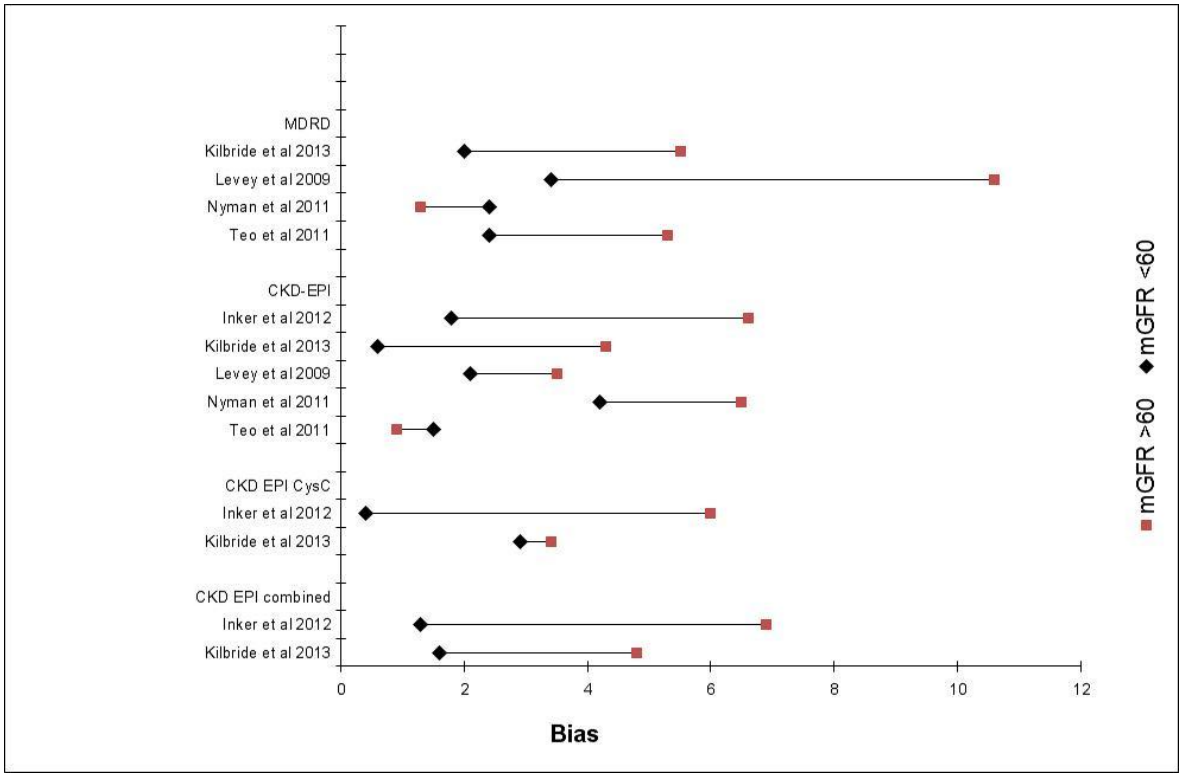


1 Teo et al 2012[670]

2 Kilbride et al 2013[341]

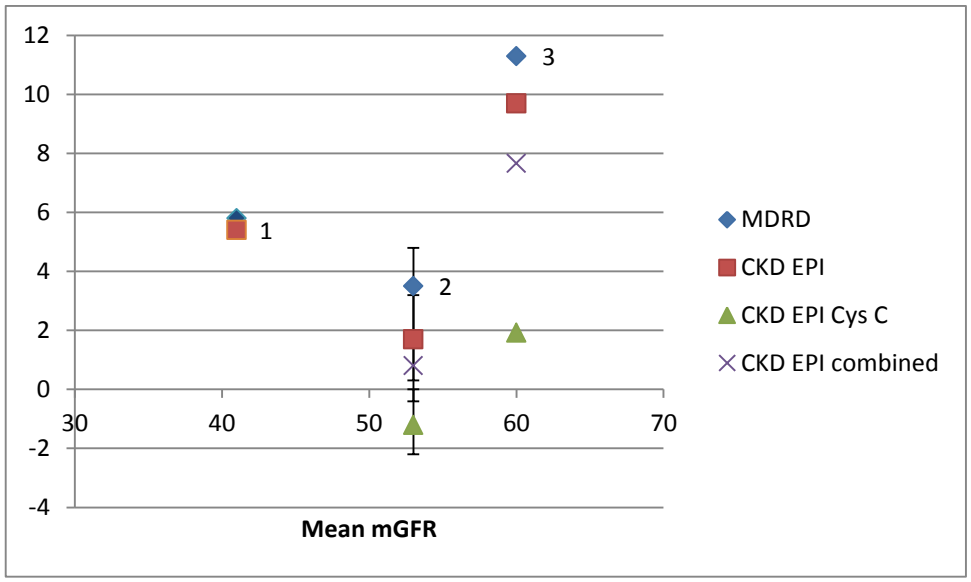
3 Schaeffner et al 2012[612]
4 Inker et al 2012[299]

Figure 21: Overall bias mGFR subgroups



Note negative signs removed i.e. direction of bias not shown

Figure 22: Bias – subgroup older people



1 Koppe et al 2013[352]

2 Kilbride et al 2013[341]

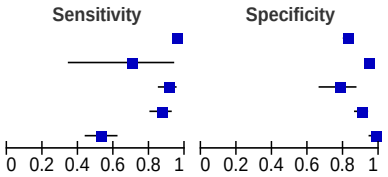
3 Schaeffner et al 2012[612]

I.1.3 Sensitivity and specificity

Figure 23: Sensitivity and specificity MDRD versus CKD EPI (sCr) (threshold GFR 60ml/min/1.73m^2) – studies in order of increasing mean age

MDRD

Study	TP	FP	FN	TN	Age	mGFR	Sensitivity	Specificity
Levey 2009	1760	265	92	1208	50.0	68.0	0.95 [0.94, 0.96]	0.82 [0.80, 0.84]
Murata 2011	7	34	3	539	56.0	55.9	0.70 [0.35, 0.93]	0.94 [0.92, 0.96]
Teo 2011	145	16	15	56	58.0	51.7	0.91 [0.85, 0.95]	0.78 [0.66, 0.87]
Iliadis 2011	126	30	19	273	65.0	73.4	0.87 [0.80, 0.92]	0.90 [0.86, 0.93]
Schaeffner 2012	71	3	63	148	78.5	60.3	0.53 [0.44, 0.62]	0.98 [0.94, 1.00]



CKD EPI

Study	TP	FP	FN	TN	Age	mGFR	Sensitivity	Specificity
Levey 2009	1685	191	167	1282	50.0	68.0	0.91 [0.90, 0.92]	0.87 [0.85, 0.89]
Murata 2011	5	11	5	562	56.0	55.9	0.50 [0.19, 0.81]	0.98 [0.97, 0.99]
Teo 2011	142	11	18	61	58.0	51.7	0.89 [0.83, 0.93]	0.85 [0.74, 0.92]
Iliadis 2011	132	36	13	267	65.0	73.4	0.91 [0.85, 0.95]	0.88 [0.84, 0.92]
Schaeffner 2012	80	4	54	147	78.5	60.3	0.60 [0.51, 0.68]	0.97 [0.93, 0.99]

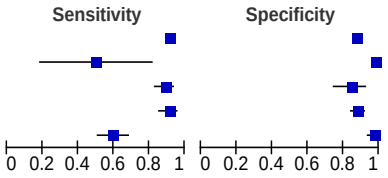
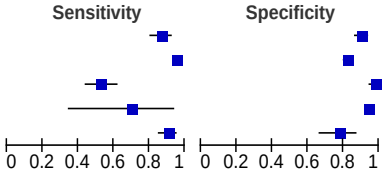


Figure 24: Sensitivity and specificity MDRD versus CKD EPI (sCr) (threshold GFR 60ml/min/1.73m^2) – studies in order of decreasing mean mGFR

MDRD

Study	TP	FP	FN	TN	Age	mGFR	Sensitivity	Specificity
Iliadis 2011	126	30	19	273	65.0	73.4	0.87 [0.80, 0.92]	0.90 [0.86, 0.93]
Levey 2009	1760	265	92	1208	50.0	68.0	0.95 [0.94, 0.96]	0.82 [0.80, 0.84]
Schaeffner 2012	71	3	63	148	78.5	60.3	0.53 [0.44, 0.62]	0.98 [0.94, 1.00]
Murata 2011	7	34	3	539	56.0	55.9	0.70 [0.35, 0.93]	0.94 [0.92, 0.96]
Teo 2011	145	16	15	56	58.0	51.7	0.91 [0.85, 0.95]	0.78 [0.66, 0.87]



CKD EPI

Study	TP	FP	FN	TN	Age	mGFR	Sensitivity	Specificity
Iliadis 2011	132	36	13	267	65.0	73.4	0.91 [0.85, 0.95]	0.88 [0.84, 0.92]
Levey 2009	1685	191	167	1282	50.0	68.0	0.91 [0.90, 0.92]	0.87 [0.85, 0.89]
Schaeffner 2012	80	4	54	147	78.5	60.3	0.60 [0.51, 0.68]	0.97 [0.93, 0.99]
Murata 2011	5	11	5	562	56.0	55.9	0.50 [0.19, 0.81]	0.98 [0.97, 0.99]
Teo 2011	142	11	18	61	58.0	51.7	0.89 [0.83, 0.93]	0.85 [0.74, 0.92]

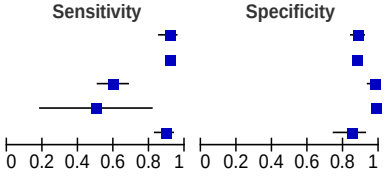
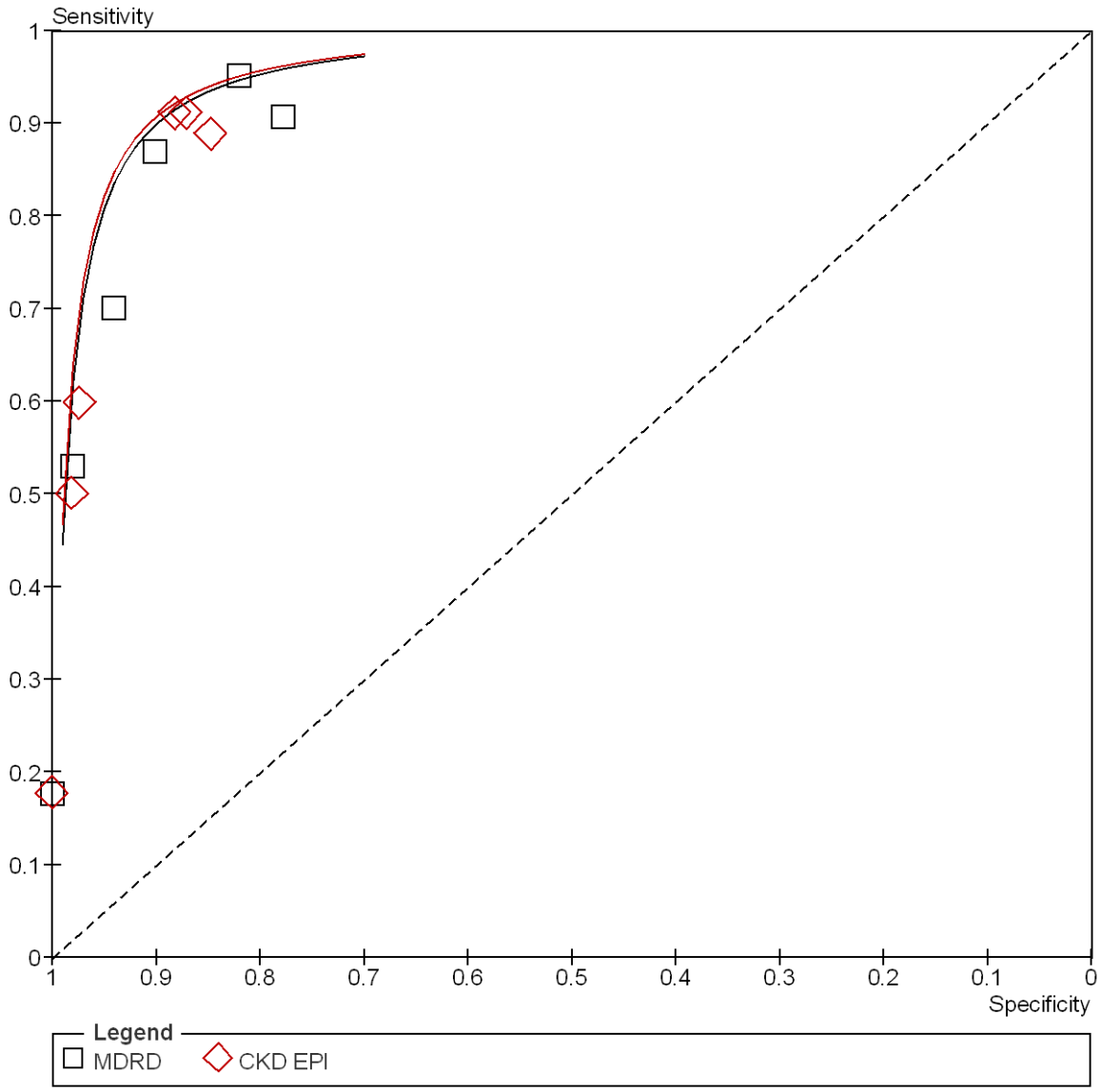


Figure 25: ROC curves MDRD versus CKD EPI (threshold mGFR 60ml/min/1.73m^2)



I.2 Markers of kidney damage

I.2.1 Combination of markers of kidney damage (multivariate analysis)

Figure 26: All-cause mortality: REGARDS

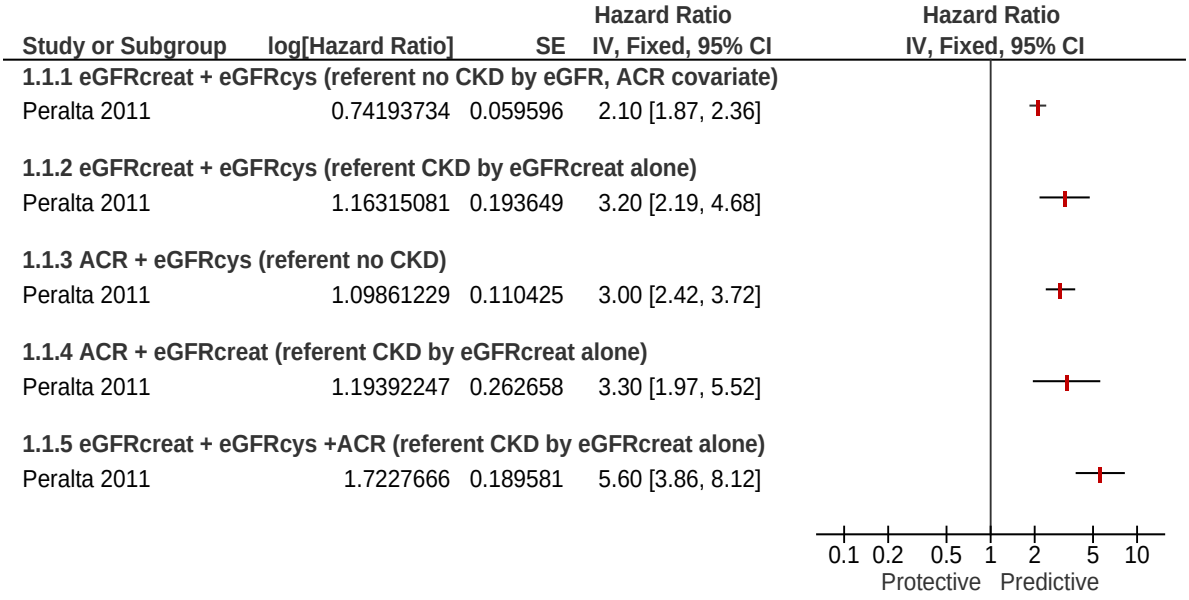


Figure 27: All cause mortality: ARIC (referent no CKD)

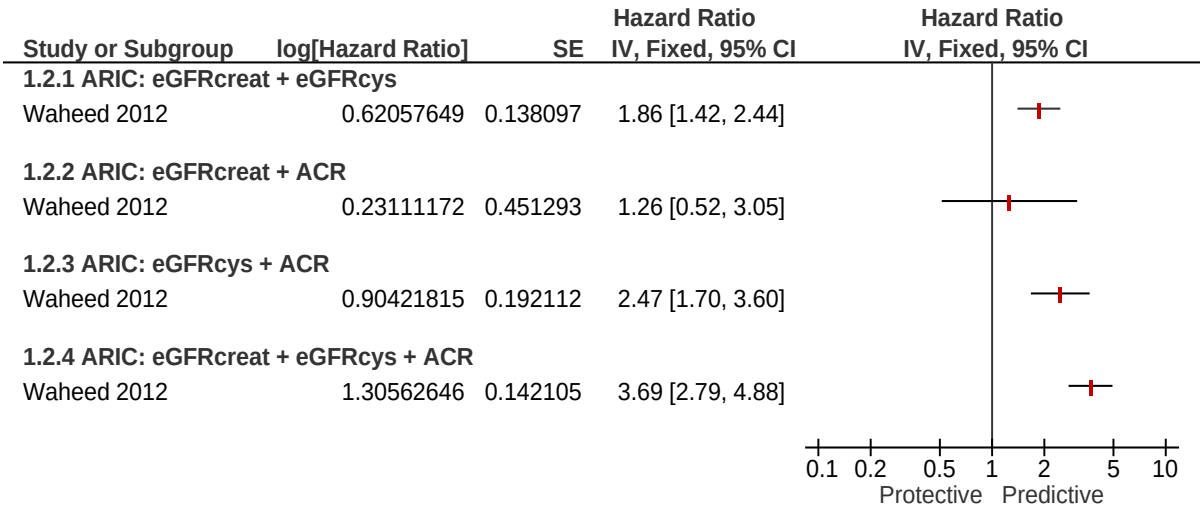


Figure 28: All-cause mortality: CHS and MESA

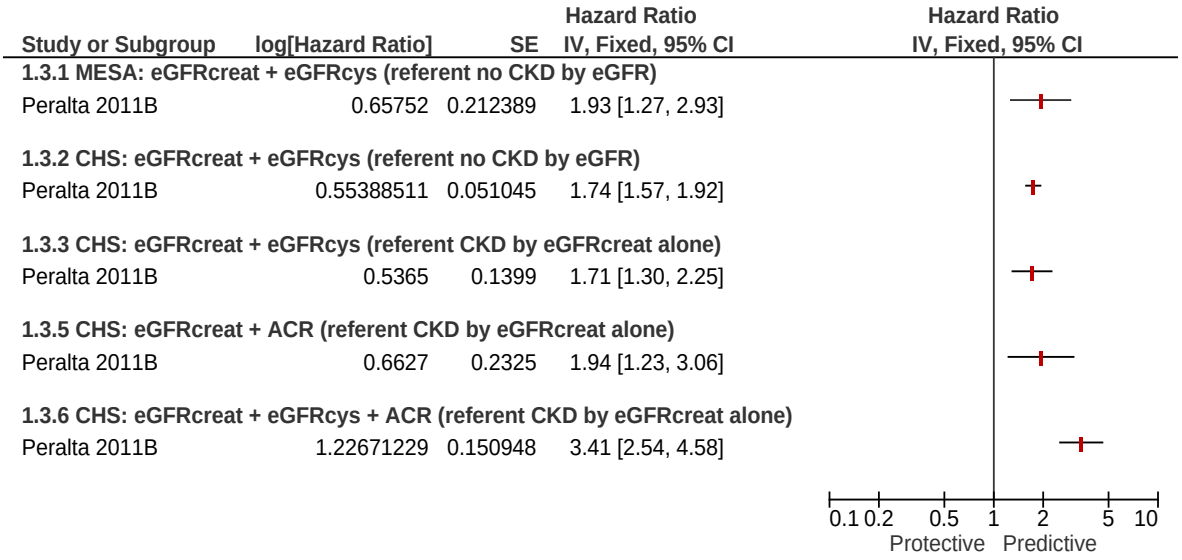


Figure 29: ESRD

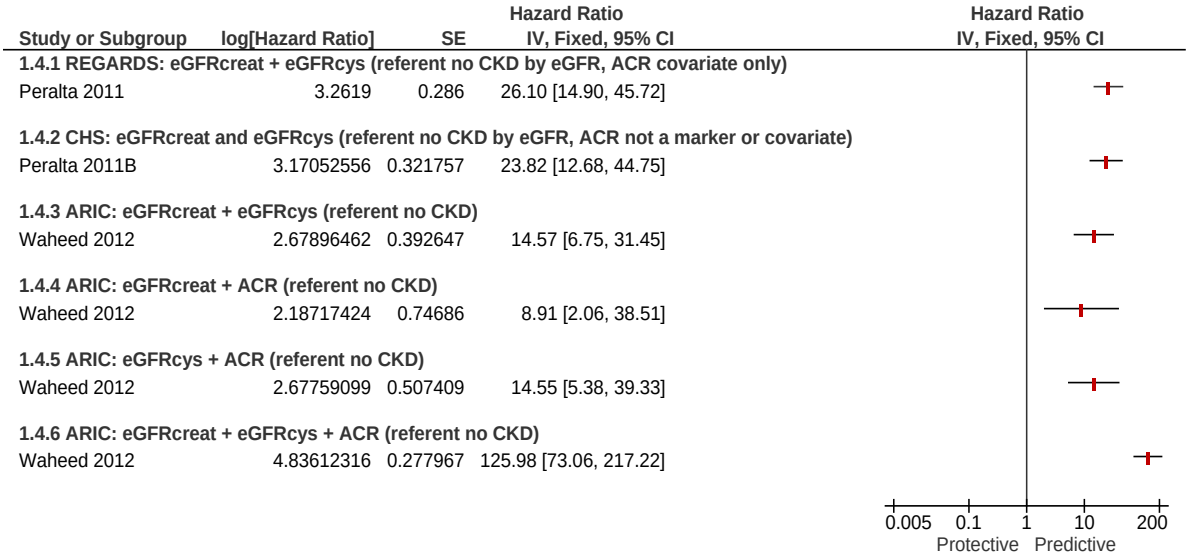


Figure 30: AKI (referent no CKD)

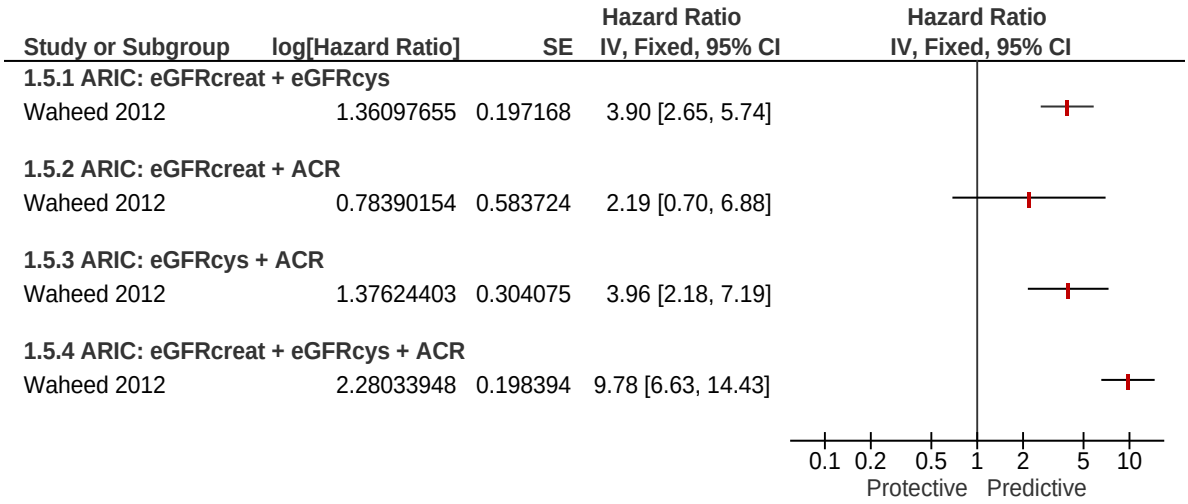


Figure 31: Cardiovascular disease

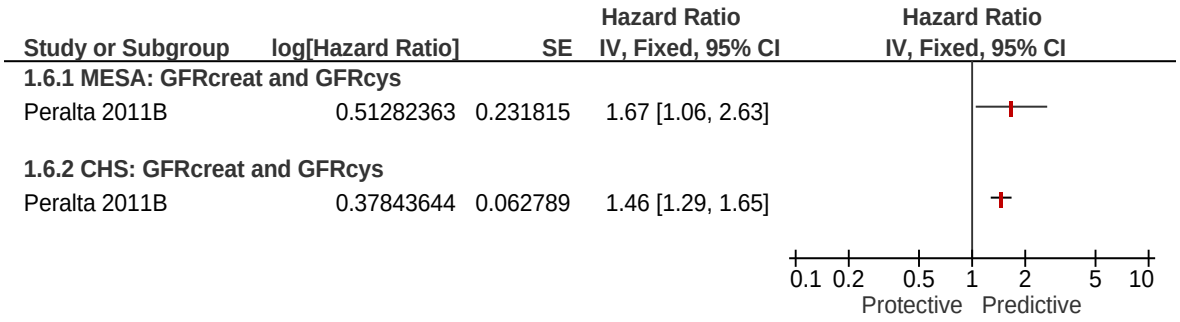


Figure 32: Coronary heart disease

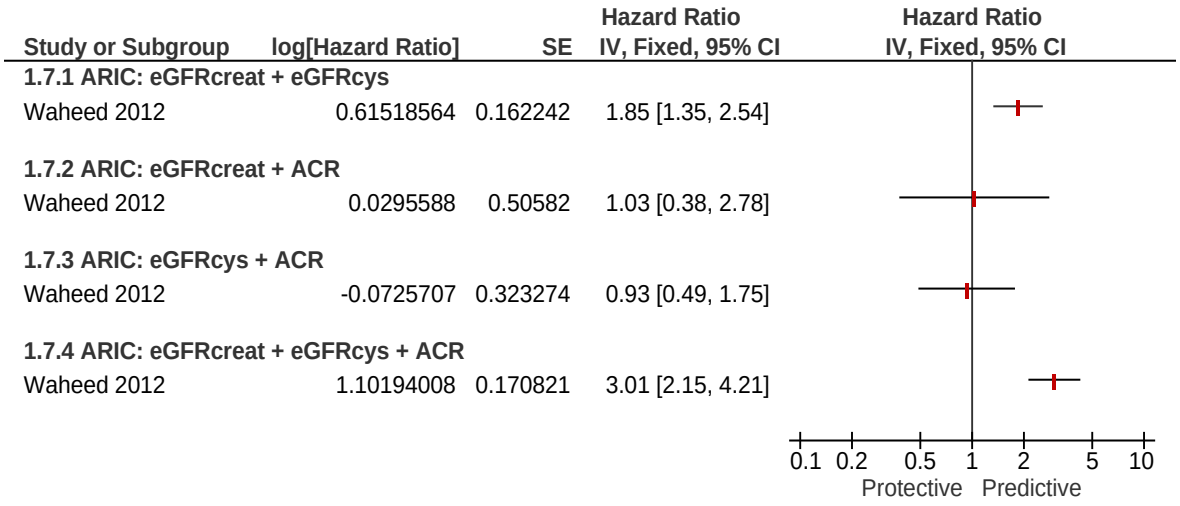
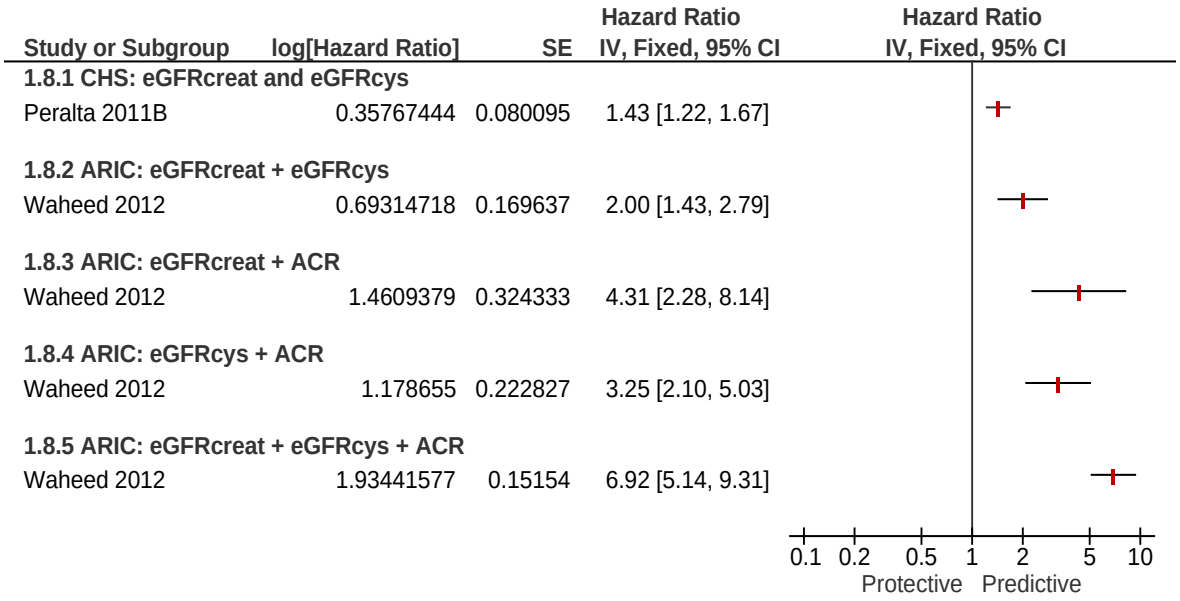


Figure 33: Heart failure



I.3 Classification of CKD

For all forest plots units are mg/g for ACR and PCR measures and ml/min/1.73m^2 for eGFR.

I.3.1 Progression of CKD

I.3.1.1 Change in eGFR

Figure 34: Change in eGFR at different ACR levels

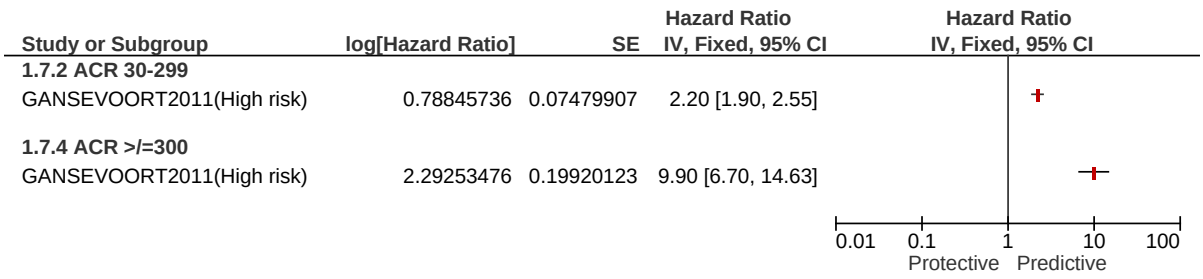
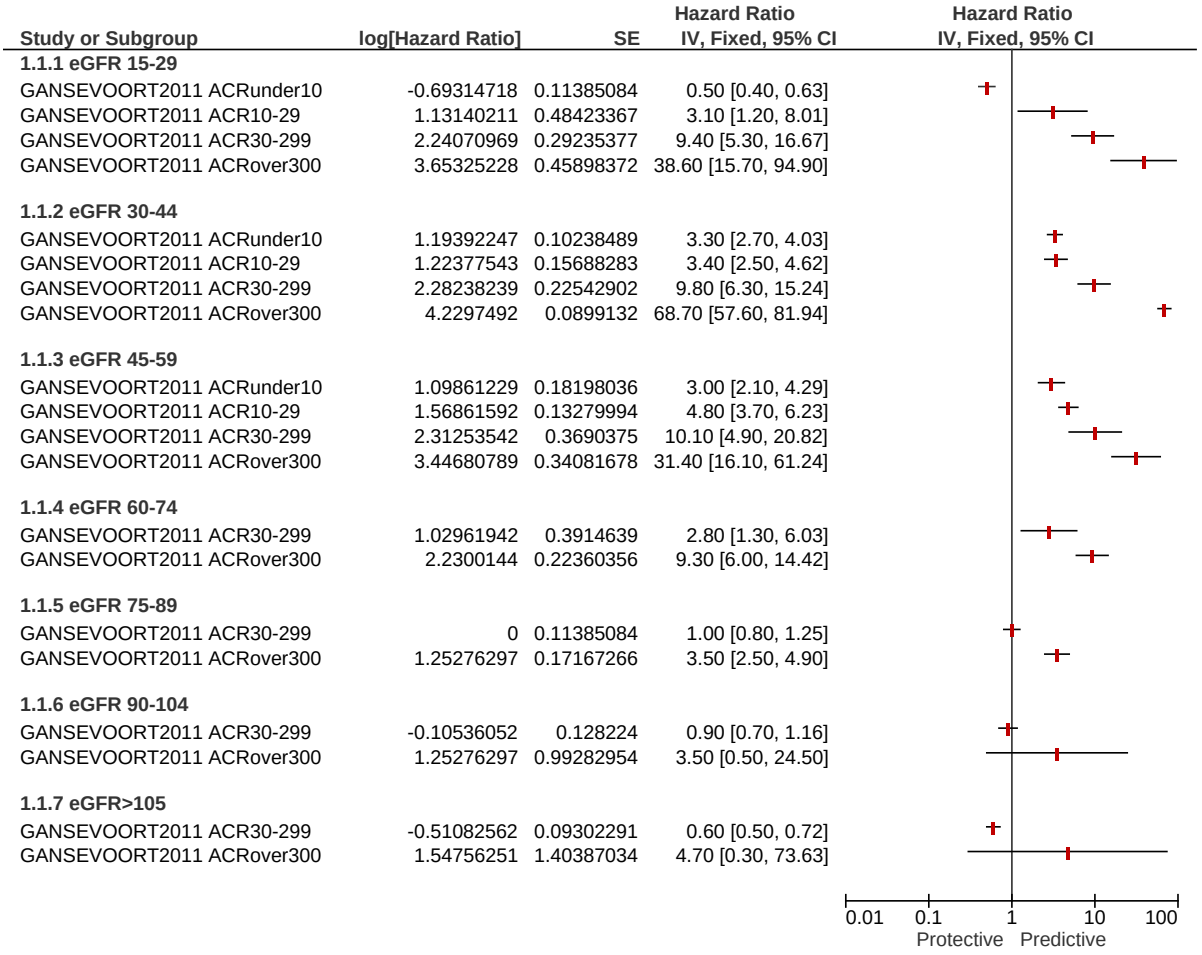


Figure 35: Change in eGFR , stratified by eGFR level



I.3.1.2 Occurrence of end stage renal disease

Figure 36: Occurrence of end stage renal disease at different PCR levels

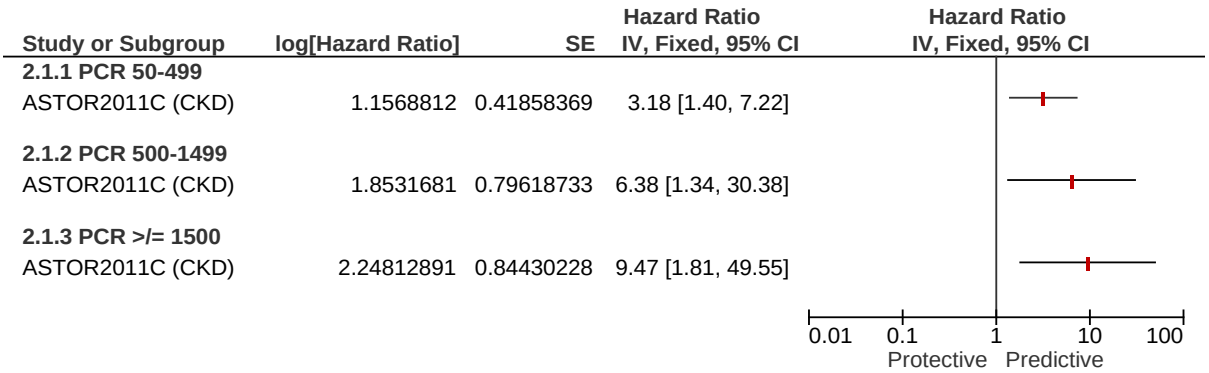


Figure 37: Occurrence of end stage renal disease at different ACR levels

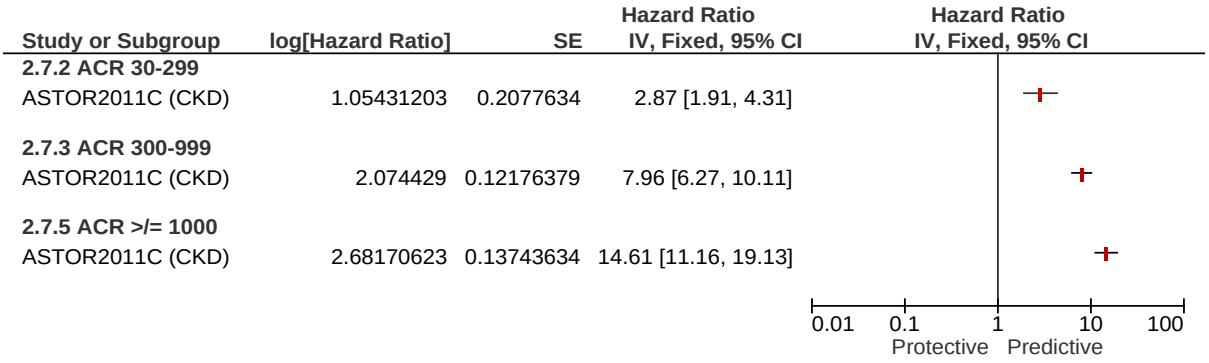
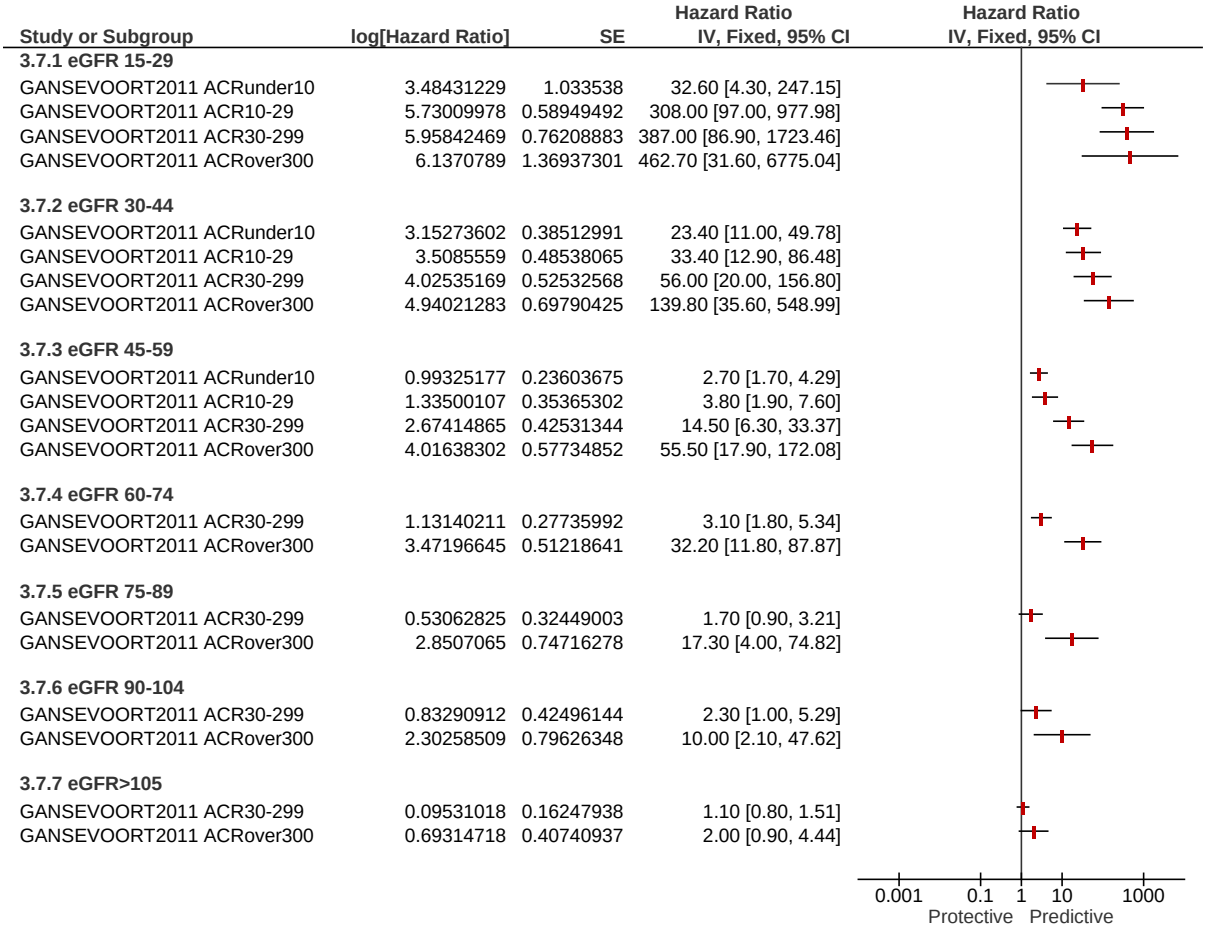


Figure 38: Occurrence of end stage renal disease stratified by eGFR



I.3.1.3 Subgroup - age

Figure 39: End stage renal disease at varying ACR levels for those <65 years and >65 years

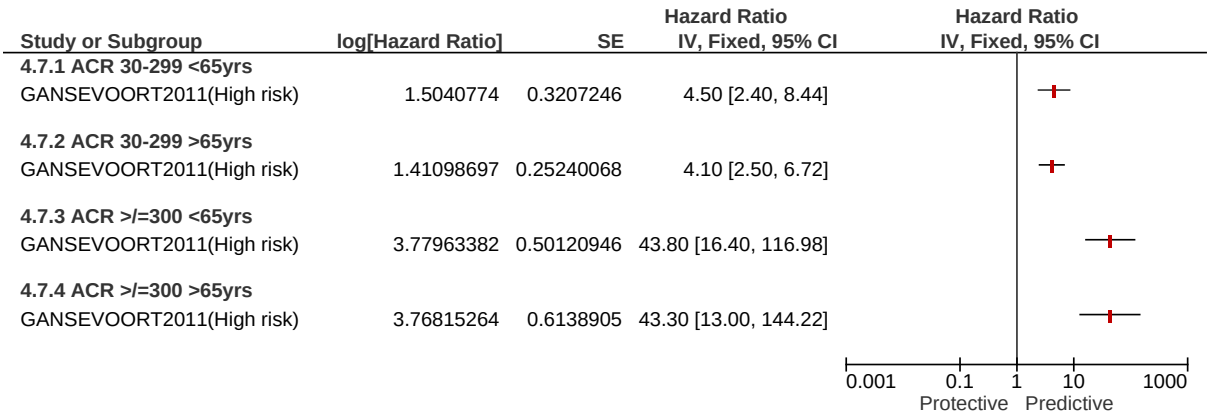
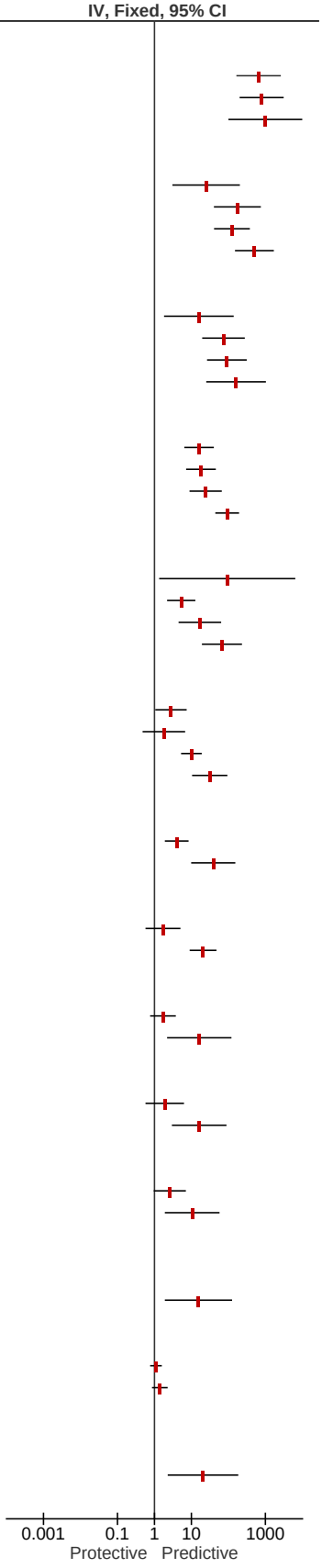


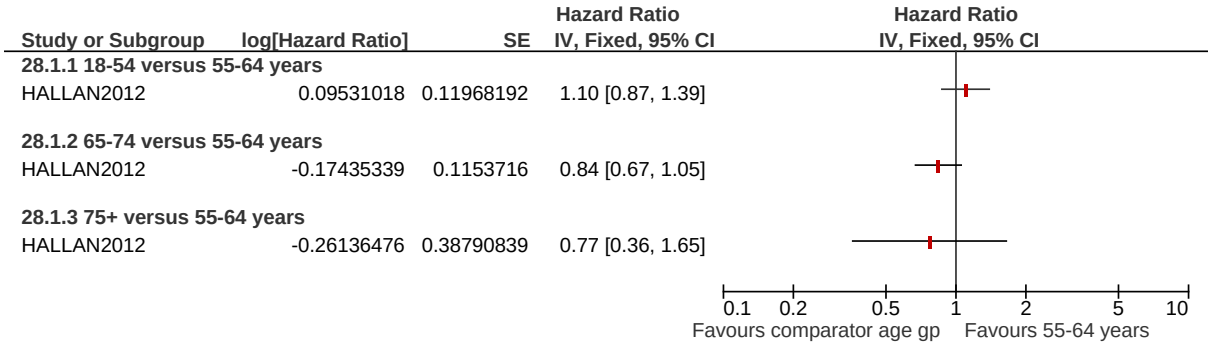
Figure 40: End stage renal disease for those <65 years and >65 years stratified by eGFR

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
6.1.1 eGFR 15-29 <65yrs			
GANSEVOORT2011 ACRunder10	0	0	Not estimable
GANSEVOORT2011 ACR10-29	6.48616079	0.68300557	656.00 [172.00, 2501.95]
GANSEVOORT2011 ACR30-299	6.67456139	0.67728482	792.00 [210.00, 2986.97]
GANSEVOORT2011 ACRover300	6.90575328	1.14889505	998.00 [105.00, 9485.75]
6.1.2 eGFR 15-29 >65yrs			
GANSEVOORT2011 ACRunder10	3.21887582	1.04885857	25.00 [3.20, 195.31]
GANSEVOORT2011 ACR10-29	5.16478597	0.72209587	175.00 [42.50, 720.59]
GANSEVOORT2011 ACR30-299	4.82831374	0.54445573	125.00 [43.00, 363.37]
GANSEVOORT2011 ACRover300	6.22653667	0.59385869	506.00 [158.00, 1620.48]
6.1.3 eGFR 30-44 <65yrs			
GANSEVOORT2011 ACRunder10	2.76631911	1.08393075	15.90 [1.90, 133.06]
GANSEVOORT2011 ACR10-29	4.29864503	0.65216512	73.60 [20.50, 264.24]
GANSEVOORT2011 ACR30-299	4.50976	0.60814599	90.90 [27.60, 299.38]
GANSEVOORT2011 ACRover300	5.08140436	0.92442282	161.00 [26.30, 985.59]
6.1.4 eGFR 30-44 >65yrs			
GANSEVOORT2011 ACRunder10	2.77881927	0.44731013	16.10 [6.70, 38.69]
GANSEVOORT2011 ACR10-29	2.89591194	0.44950261	18.10 [7.50, 43.68]
GANSEVOORT2011 ACR30-299	3.19047635	0.49004061	24.30 [9.30, 63.49]
GANSEVOORT2011 ACRover300	4.52936847	0.35420371	92.70 [46.30, 185.60]
6.1.5 eGFR 45-59 <65yrs			
GANSEVOORT2011 ACRunder10	4.52936847	2.13927208	92.70 [1.40, 6138.06]
GANSEVOORT2011 ACR10-29	1.66770682	0.42592502	5.30 [2.30, 12.21]
GANSEVOORT2011 ACR30-299	2.82731362	0.65294624	16.90 [4.70, 60.77]
GANSEVOORT2011 ACRover300	4.20319897	0.61352105	66.90 [20.10, 222.67]
6.1.6 eGFR 45-59 >65yrs			
GANSEVOORT2011 ACRunder10	1.02961942	0.47669715	2.80 [1.10, 7.13]
GANSEVOORT2011 ACR10-29	0.58778666	0.65354969	1.80 [0.50, 6.48]
GANSEVOORT2011 ACR30-299	2.30258509	0.30502448	10.00 [5.50, 18.18]
GANSEVOORT2011 ACRover300	3.44041809	0.53656869	31.20 [10.90, 89.31]
6.1.7 eGFR 60-74 <65yrs			
GANSEVOORT2011 ACR30-299	1.38629436	0.35365302	4.00 [2.00, 8.00]
GANSEVOORT2011 ACRover300	3.66356165	0.67930725	39.00 [10.30, 147.67]
6.1.8 eGFR 60-74 >65yrs			
GANSEVOORT2011 ACR30-299	0.53062825	0.53136378	1.70 [0.60, 4.82]
GANSEVOORT2011 ACRover300	3.0301337	0.40277475	20.70 [9.40, 45.58]
6.1.9 eGFR 75-89 <65yrs			
GANSEVOORT2011 ACR30-299	0.53062825	0.38458452	1.70 [0.80, 3.61]
GANSEVOORT2011 ACRover300	2.79116511	0.99912856	16.30 [2.30, 115.52]
6.1.10 eGFR 75-89 >65yrs			
GANSEVOORT2011 ACR30-299	0.64185389	0.5881126	1.90 [0.60, 6.02]
GANSEVOORT2011 ACRover300	2.78501124	0.84369363	16.20 [3.10, 84.66]
6.1.11 eGFR 90-104 <65yrs			
GANSEVOORT2011 ACR30-299	0.95551145	0.4875148	2.60 [1.00, 6.76]
GANSEVOORT2011 ACRover300	2.35137526	0.84605028	10.50 [2.00, 55.12]
6.1.12 eGFR 90-104 >65yrs			
GANSEVOORT2011 ACR30-299	0	0	Not estimable
GANSEVOORT2011 ACRover300	2.74084002	1.04476044	15.50 [2.00, 120.12]
6.1.13 eGFR>105 <65yrs			
GANSEVOORT2011 ACR30-299	0.09531018	0.16247938	1.10 [0.80, 1.51]
GANSEVOORT2011 ACRover300	0.33647224	0.22542902	1.40 [0.90, 2.18]
6.1.14 eGFR>105 >65yrs			
GANSEVOORT2011 ACR30-299	0	0	Not estimable
GANSEVOORT2011 ACRover300	3.02529108	1.09686829	20.60 [2.40, 176.82]



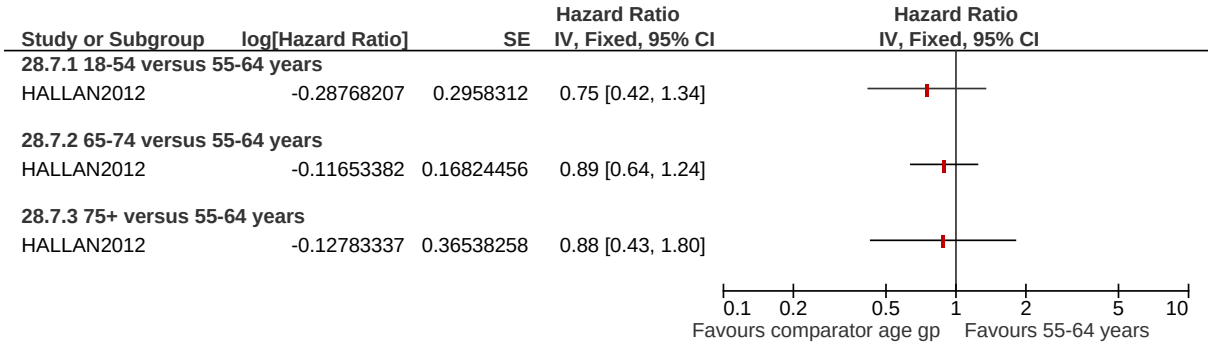
I.3.1.4 Subgroup - age interaction with eGFR (per 15ml/min/1.73m^2 decline)

Figure 41: End stage renal disease – Age interaction with eGFR



I.3.1.5 Subgroup - age interaction with ACR (according to 10-fold higher ACR)

Figure 42: End stage renal disease – Age interaction with ACR



I.3.1.6 Subgroup – diabetes

Figure 43: End stage renal disease at varying ACR levels for those with and without diabetes

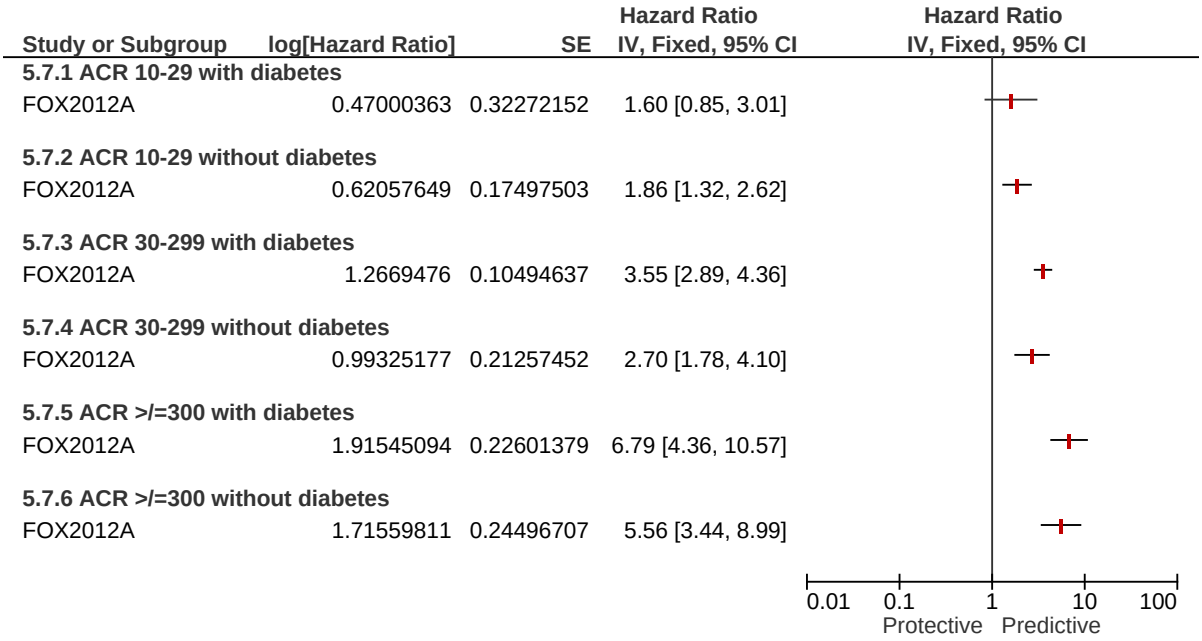
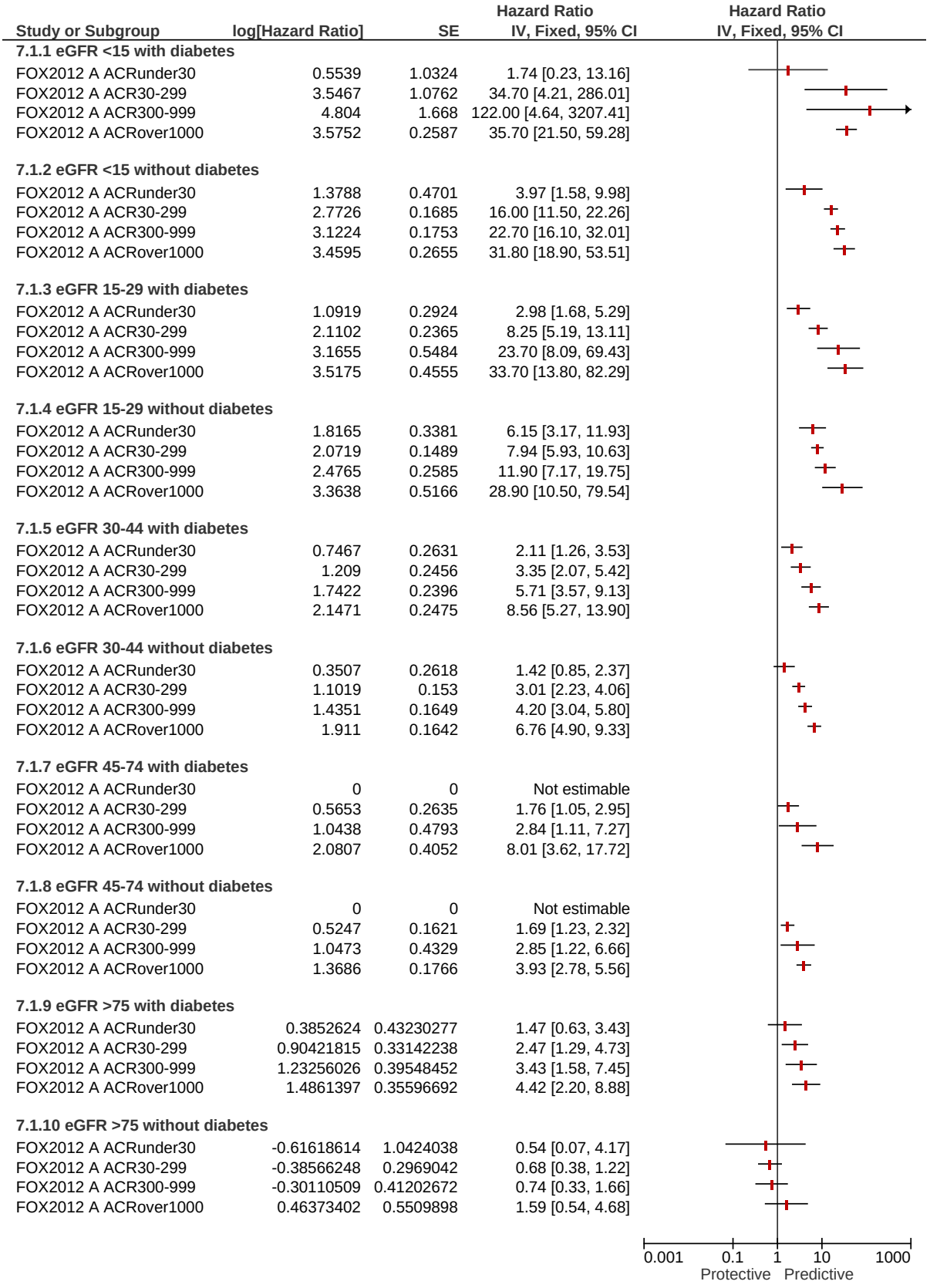


Figure 44: End stage renal disease stratified by eGFR for those with and without diabetes



I.3.1.7 Subgroup – hypertension

Figure 45: End stage renal disease at varying ACR levels for those with and without hypertension

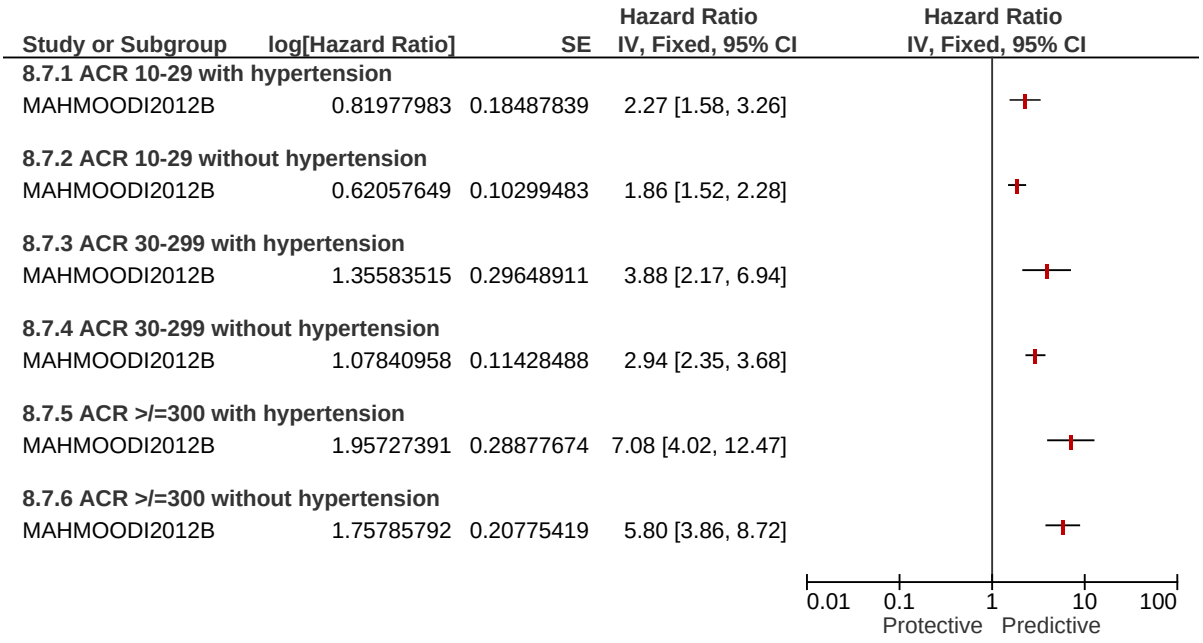
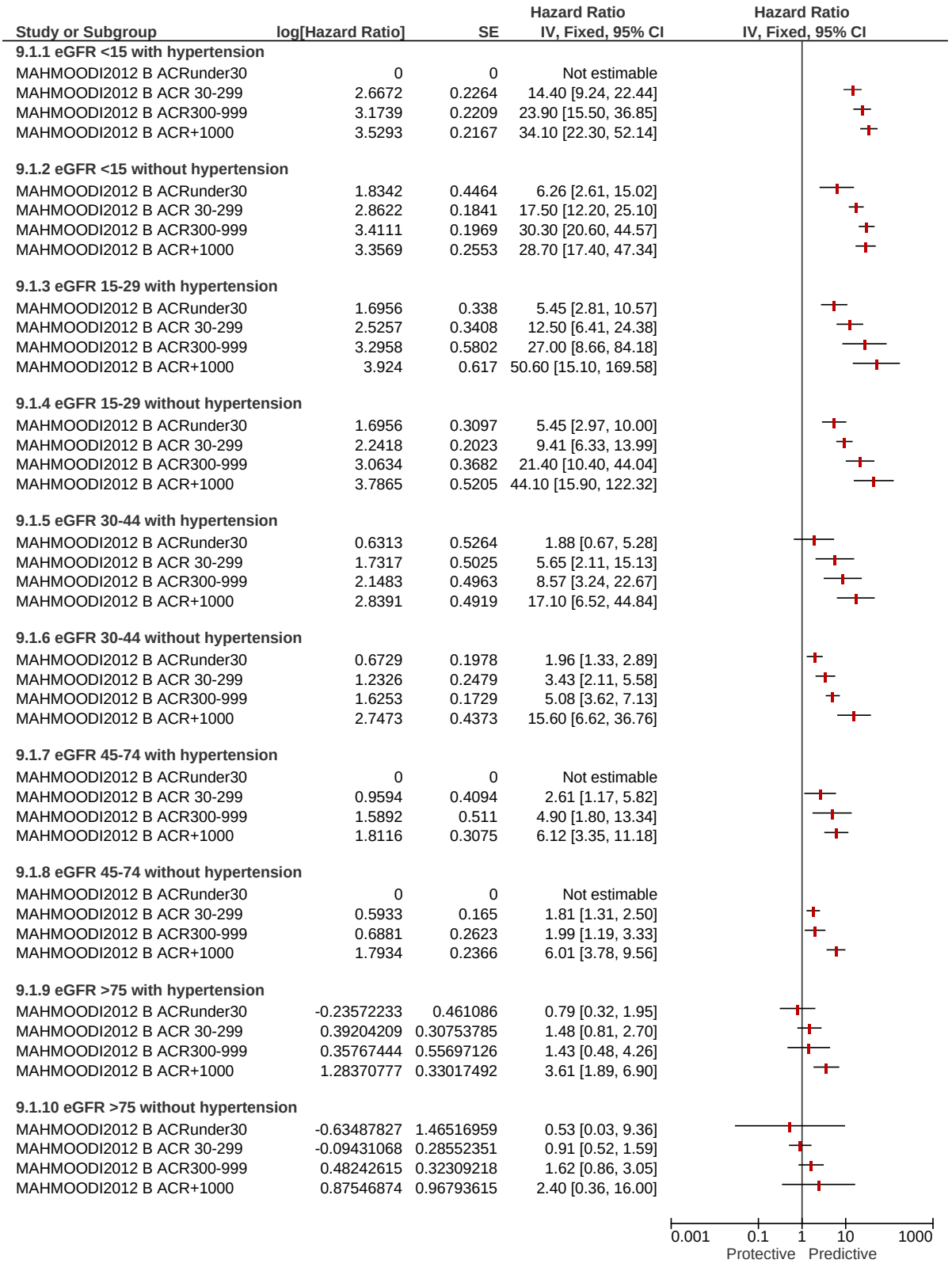


Figure 46: End stage renal disease stratified by eGFR for those with and without hypertension



I.3.2 All-cause mortality

Figure 47: All-cause mortality at different PCR levels

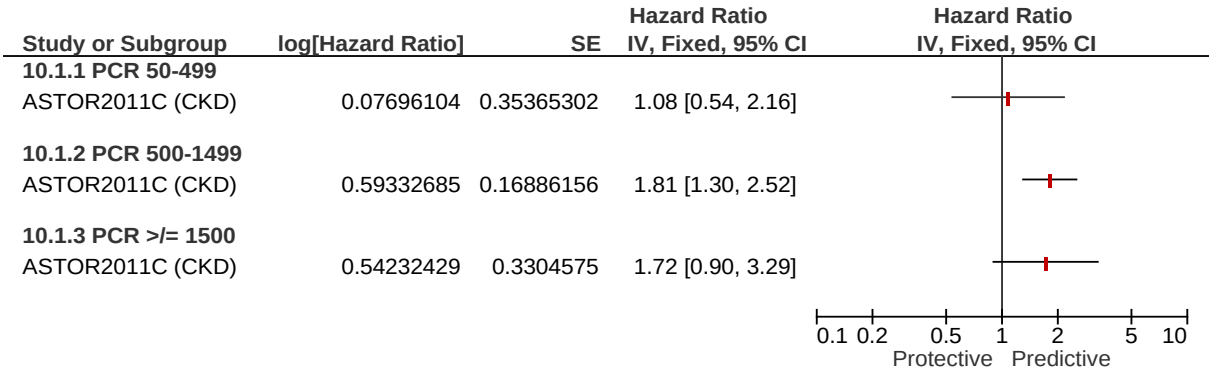


Figure 48: All-cause mortality at different ACR levels

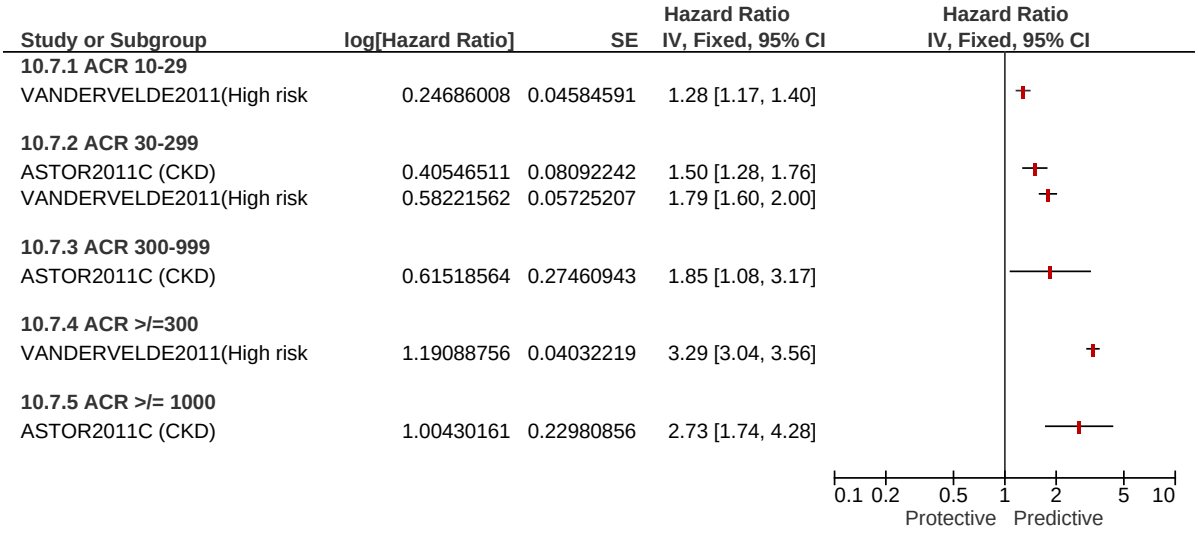
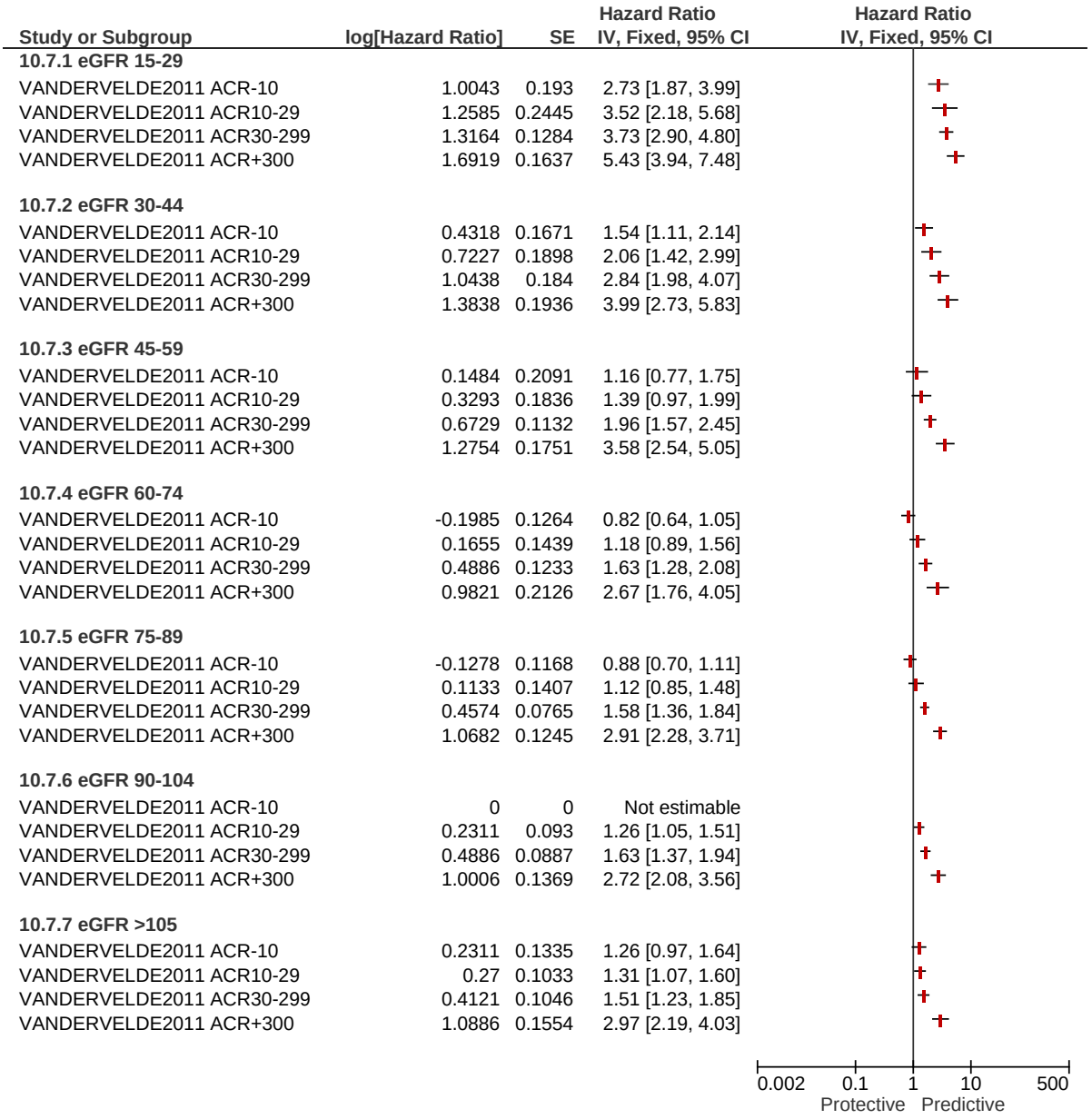


Figure 49: All-cause mortality stratified by eGFR



I.3.2.1 Subgroup - age

Figure 50: All-cause mortality at varying ACR levels for those <65 years and >65 years

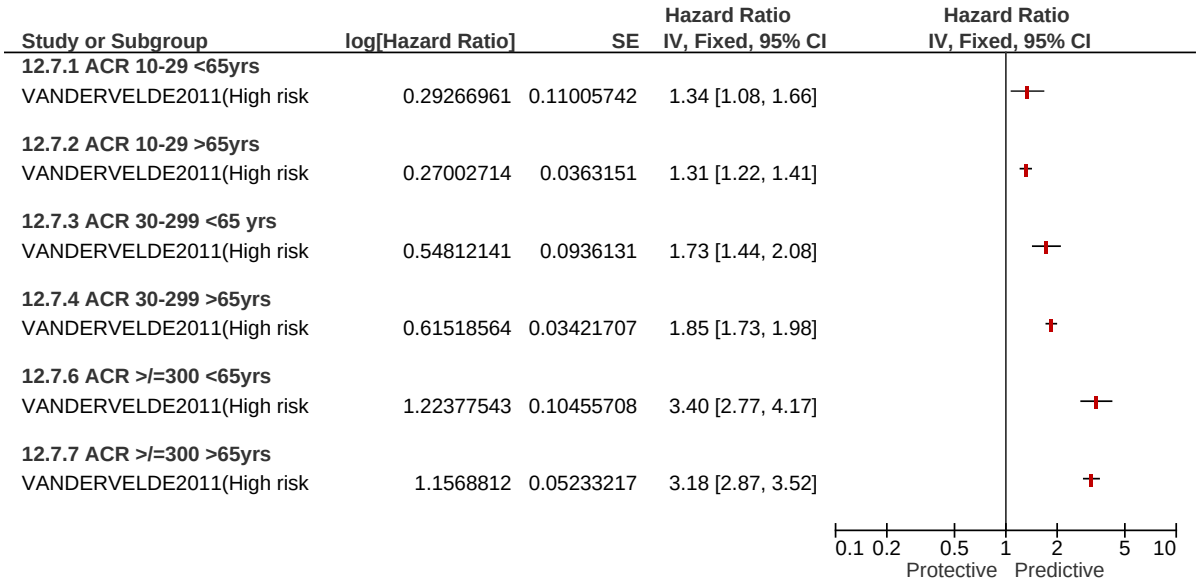
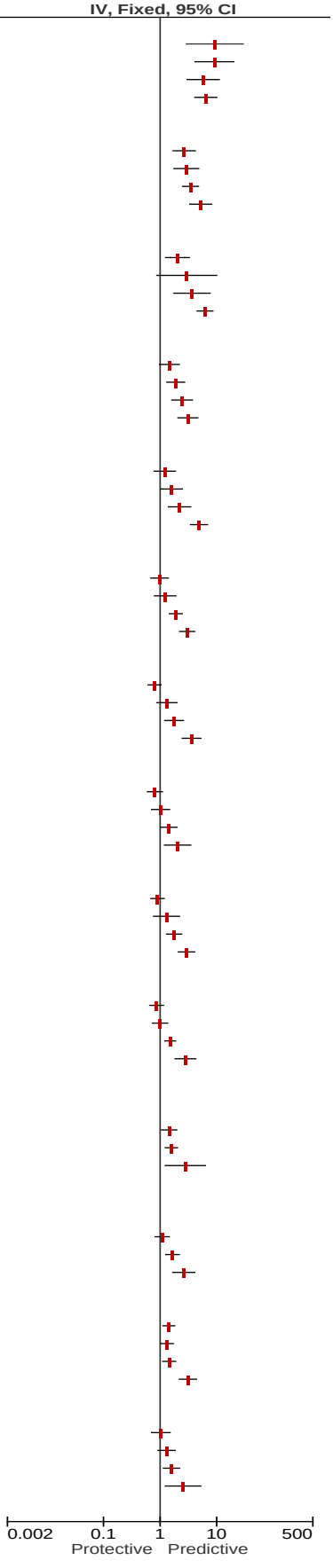


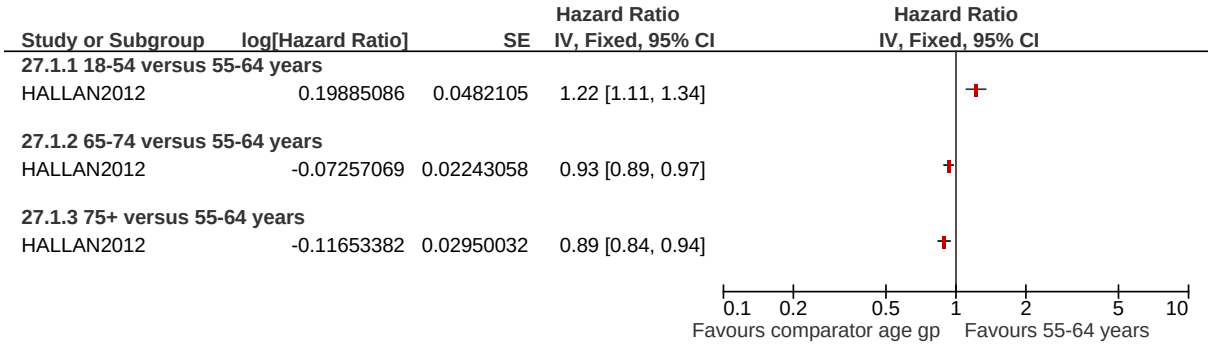
Figure 51: All-cause mortality by age, stratified by eGFR

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
12.1.1 eGFR 15-29 <65yrs			
VANDERVELDE2011 ACR-10	2.2268	0.5894	9.27 [2.92, 29.43]
VANDERVELDE2011 ACR10-29	2.2148	0.3991	9.16 [4.19, 20.03]
VANDERVELDE2011 ACR30-299	1.7561	0.3304	5.79 [3.03, 11.06]
VANDERVELDE2011 ACR+300	1.8594	0.2263	6.42 [4.12, 10.00]
12.1.2 eGFR 15-29 >65yrs			
VANDERVELDE2011 ACR-10	0.9821	0.2273	2.67 [1.71, 4.17]
VANDERVELDE2011 ACR10-29	1.0682	0.2537	2.91 [1.77, 4.78]
VANDERVELDE2011 ACR30-299	1.2413	0.1617	3.46 [2.52, 4.75]
VANDERVELDE2011 ACR+300	1.6525	0.2248	5.22 [3.36, 8.11]
12.1.3 eGFR 30-44 <65yrs			
VANDERVELDE2011 ACR-10	0.708	0.2433	2.03 [1.26, 3.27]
VANDERVELDE2011 ACR10-29	1.0852	0.6189	2.96 [0.88, 9.96]
VANDERVELDE2011 ACR30-299	1.3002	0.3721	3.67 [1.77, 7.61]
VANDERVELDE2011 ACR+300	1.8278	0.1606	6.22 [4.54, 8.52]
12.1.4 eGFR 30-44 >65yrs			
VANDERVELDE2011 ACR-10	0.3784	0.2034	1.46 [0.98, 2.18]
VANDERVELDE2011 ACR10-29	0.6366	0.1831	1.89 [1.32, 2.71]
VANDERVELDE2011 ACR30-299	0.8961	0.2111	2.45 [1.62, 3.71]
VANDERVELDE2011 ACR+300	1.1314	0.2036	3.10 [2.08, 4.62]
12.1.5 eGFR 45-59 <65yrs			
VANDERVELDE2011 ACR-10	0.1906	0.2175	1.21 [0.79, 1.85]
VANDERVELDE2011 ACR10-29	0.47	0.2198	1.60 [1.04, 2.46]
VANDERVELDE2011 ACR30-299	0.793	0.2293	2.21 [1.41, 3.46]
VANDERVELDE2011 ACR+300	1.5851	0.174	4.88 [3.47, 6.86]
12.1.6 eGFR 45-59 >65yrs			
VANDERVELDE2011 ACR-10	-0.0202	0.179	0.98 [0.69, 1.39]
VANDERVELDE2011 ACR10-29	0.207	0.2195	1.23 [0.80, 1.89]
VANDERVELDE2011 ACR30-299	0.6419	0.1309	1.90 [1.47, 2.46]
VANDERVELDE2011 ACR+300	1.1019	0.1553	3.01 [2.22, 4.08]
12.1.7 eGFR 60-74 <65yrs			
VANDERVELDE2011 ACR-10	-0.2231	0.13	0.80 [0.62, 1.03]
VANDERVELDE2011 ACR10-29	0.2776	0.2069	1.32 [0.88, 1.98]
VANDERVELDE2011 ACR30-299	0.571	0.1899	1.77 [1.22, 2.57]
VANDERVELDE2011 ACR+300	1.2809	0.1901	3.60 [2.48, 5.23]
12.1.8 eGFR 60-74 >65yrs			
VANDERVELDE2011 ACR-10	-0.2107	0.1531	0.81 [0.60, 1.09]
VANDERVELDE2011 ACR10-29	0.0198	0.1848	1.02 [0.71, 1.47]
VANDERVELDE2011 ACR30-299	0.3577	0.1674	1.43 [1.03, 1.99]
VANDERVELDE2011 ACR+300	0.7129	0.2707	2.04 [1.20, 3.47]
12.1.9 eGFR 75-89 <65yrs			
VANDERVELDE2011 ACR-10	-0.1054	0.1356	0.90 [0.69, 1.17]
VANDERVELDE2011 ACR10-29	0.2624	0.2672	1.30 [0.77, 2.19]
VANDERVELDE2011 ACR30-299	0.571	0.1535	1.77 [1.31, 2.39]
VANDERVELDE2011 ACR+300	1.0716	0.1658	2.92 [2.11, 4.04]
12.1.10 eGFR 75-89 >65yrs			
VANDERVELDE2011 ACR-10	-0.1393	0.1409	0.87 [0.66, 1.15]
VANDERVELDE2011 ACR10-29	0	0.1536	1.00 [0.74, 1.35]
VANDERVELDE2011 ACR30-299	0.4121	0.1088	1.51 [1.22, 1.87]
VANDERVELDE2011 ACR+300	1.0332	0.2105	2.81 [1.86, 4.25]
12.1.11 eGFR 90-104 <65yrs			
VANDERVELDE2011 ACR-10	0	0	Not estimable
VANDERVELDE2011 ACR10-29	0.3716	0.1551	1.45 [1.07, 1.97]
VANDERVELDE2011 ACR30-299	0.4574	0.1236	1.58 [1.24, 2.01]
VANDERVELDE2011 ACR+300	1.026	0.4137	2.79 [1.24, 6.28]
12.1.12 eGFR 90-104 >65yrs			
VANDERVELDE2011 ACR-10	0	0	Not estimable
VANDERVELDE2011 ACR10-29	0.0862	0.1452	1.09 [0.82, 1.45]
VANDERVELDE2011 ACR30-299	0.5068	0.1366	1.66 [1.27, 2.17]
VANDERVELDE2011 ACR+300	0.9632	0.2267	2.62 [1.68, 4.09]
12.1.13 eGFR >105 <65yrs			
VANDERVELDE2011 ACR-10	0.3577	0.1201	1.43 [1.13, 1.81]
VANDERVELDE2011 ACR10-29	0.2852	0.1255	1.33 [1.04, 1.70]
VANDERVELDE2011 ACR30-299	0.3716	0.1318	1.45 [1.12, 1.88]
VANDERVELDE2011 ACR+300	1.1314	0.175	3.10 [2.20, 4.37]
12.1.14 eGFR >105 >65yrs			
VANDERVELDE2011 ACR-10	0.0296	0.1898	1.03 [0.71, 1.49]
VANDERVELDE2011 ACR10-29	0.2624	0.1764	1.30 [0.92, 1.84]
VANDERVELDE2011 ACR30-299	0.4637	0.1653	1.59 [1.15, 2.20]
VANDERVELDE2011 ACR+300	0.9322	0.3658	2.54 [1.24, 5.20]



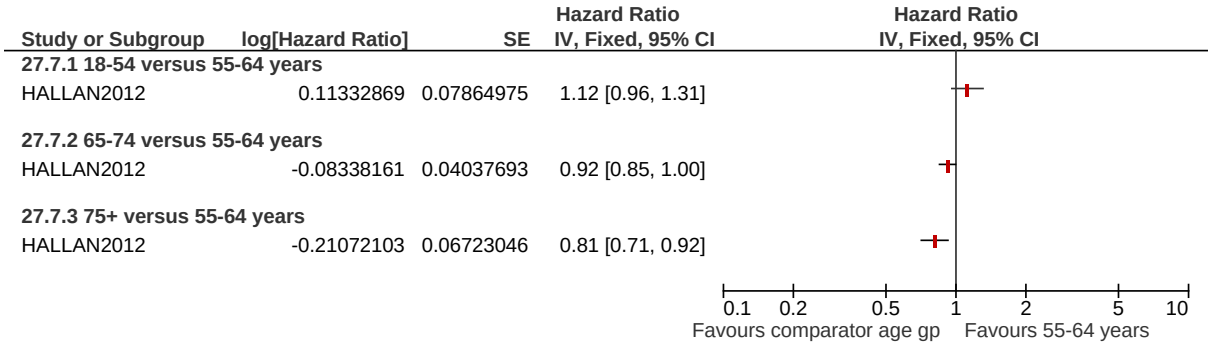
I.3.2.2 Subgroup - age interaction with eGFR (per 15ml/min/1.73m^2 decline)

Figure 52: All-cause mortality – age interaction with eGFR



I.3.2.3 Subgroup - age interaction with ACR (according to 10 fold higher ACR)

Figure 53: All-cause mortality – age interaction with ACR



I.3.2.4 Subgroup – diabetes

Figure 54: All-cause mortality at varying ACR levels for those with and without diabetes

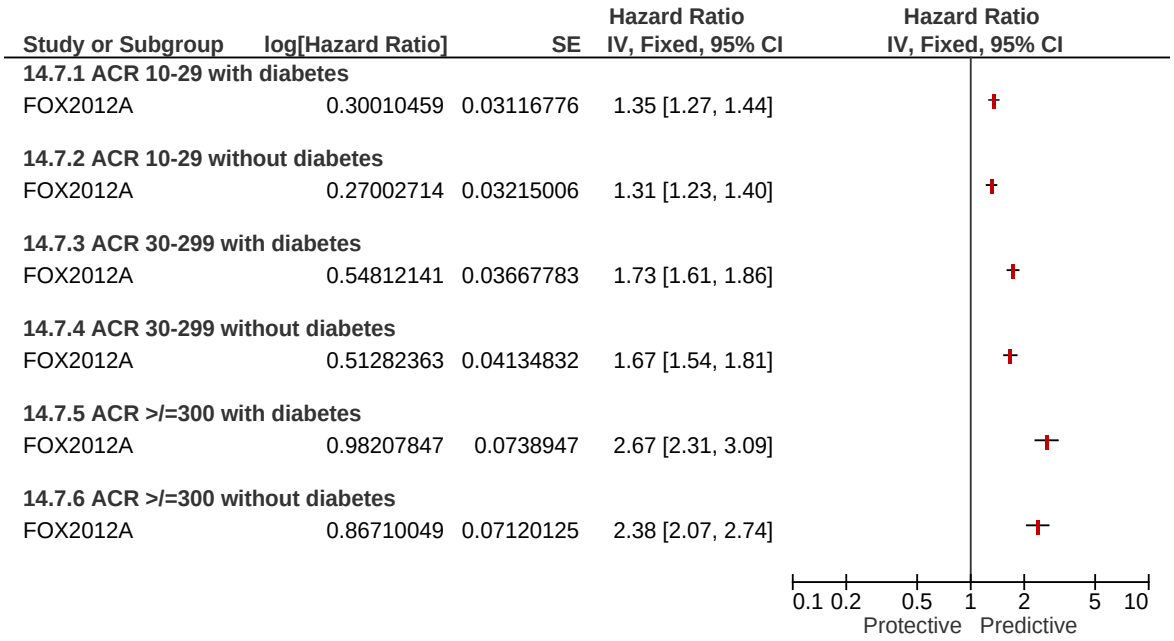
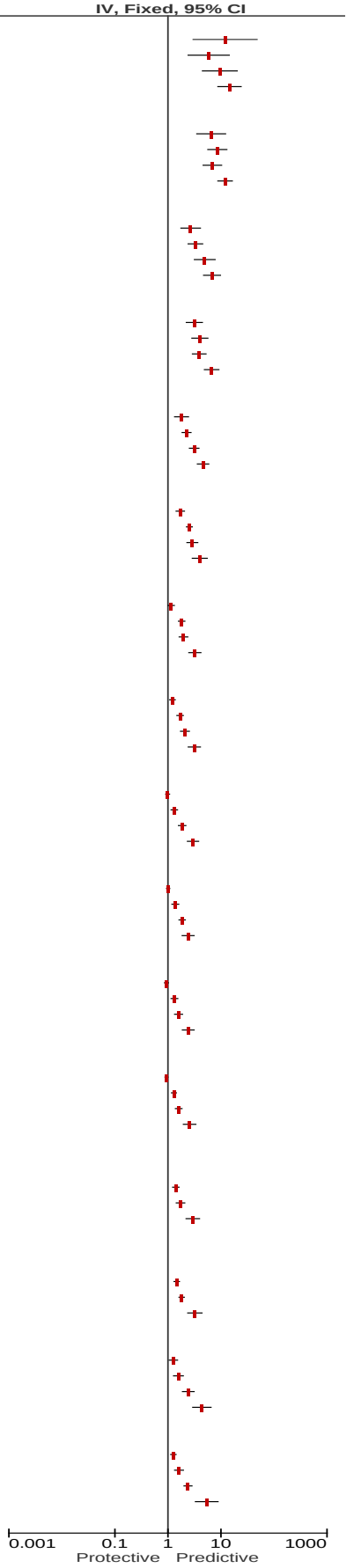


Figure 55: All-cause mortality stratified by eGFR for those with and without diabetes

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
14.1.1 eGFR <15 with diabetes			
FOX2012 A ACRunder10	2.4849	0.7039	12.00 [3.02, 47.68]
FOX2012 A ACR10-29	1.7716	0.4509	5.88 [2.43, 14.23]
FOX2012 A ACR30-299	2.2565	0.3805	9.55 [4.53, 20.13]
FOX2012 A ACRover300	2.6741	0.2525	14.50 [8.84, 23.78]
14.1.2 eGFR <15 without diabetes			
FOX2012 A ACRunder10	1.8795	0.3154	6.55 [3.53, 12.15]
FOX2012 A ACR10-29	2.1471	0.2057	8.56 [5.72, 12.81]
FOX2012 A ACR30-299	1.933	0.1999	6.91 [4.67, 10.22]
FOX2012 A ACRover300	2.4849	0.1559	12.00 [8.84, 16.29]
14.1.3 eGFR 15-29 with diabetes			
FOX2012 A ACRunder10	0.9895	0.2107	2.69 [1.78, 4.07]
FOX2012 A ACR10-29	1.1939	0.1561	3.30 [2.43, 4.48]
FOX2012 A ACR30-299	1.6014	0.2252	4.96 [3.19, 7.71]
FOX2012 A ACRover300	1.9169	0.182	6.80 [4.76, 9.71]
14.1.4 eGFR 15-29 without diabetes			
FOX2012 A ACRunder10	1.1506	0.1733	3.16 [2.25, 4.44]
FOX2012 A ACR10-29	1.3888	0.1724	4.01 [2.86, 5.62]
FOX2012 A ACR30-299	1.361	0.1459	3.90 [2.93, 5.19]
FOX2012 A ACRover300	1.9006	0.1547	6.69 [4.94, 9.06]
14.1.5 eGFR 30-44 with diabetes			
FOX2012 A ACRunder10	0.5933	0.1496	1.81 [1.35, 2.43]
FOX2012 A ACR10-29	0.8109	0.0944	2.25 [1.87, 2.71]
FOX2012 A ACR30-299	1.141	0.1006	3.13 [2.57, 3.81]
FOX2012 A ACRover300	1.5282	0.1205	4.61 [3.64, 5.84]
14.1.6 eGFR 30-44 without diabetes			
FOX2012 A ACRunder10	0.5365	0.0877	1.71 [1.44, 2.03]
FOX2012 A ACR10-29	0.9322	0.0596	2.54 [2.26, 2.85]
FOX2012 A ACR30-299	1.0613	0.1143	2.89 [2.31, 3.62]
FOX2012 A ACRover300	1.3863	0.1606	4.00 [2.92, 5.48]
14.1.7 eGFR 45-59 with diabetes			
FOX2012 A ACRunder10	0.1398	0.0662	1.15 [1.01, 1.31]
FOX2012 A ACR10-29	0.5988	0.0657	1.82 [1.60, 2.07]
FOX2012 A ACR30-299	0.678	0.0904	1.97 [1.65, 2.35]
FOX2012 A ACRover300	1.1725	0.1287	3.23 [2.51, 4.16]
14.1.8 eGFR 45-59 without diabetes			
FOX2012 A ACRunder10	0.1989	0.0575	1.22 [1.09, 1.37]
FOX2012 A ACR10-29	0.5306	0.0673	1.70 [1.49, 1.94]
FOX2012 A ACR30-299	0.7419	0.093	2.10 [1.75, 2.52]
FOX2012 A ACRover300	1.1474	0.1303	3.15 [2.44, 4.07]
14.1.9 eGFR 60-74 with diabetes			
FOX2012 A ACRunder10	-0.0101	0.0374	0.99 [0.92, 1.07]
FOX2012 A ACR10-29	0.2776	0.0659	1.32 [1.16, 1.50]
FOX2012 A ACR30-299	0.6206	0.0768	1.86 [1.60, 2.16]
FOX2012 A ACRover300	1.0919	0.119	2.98 [2.36, 3.76]
14.1.10 eGFR 60-74 without diabetes			
FOX2012 A ACRunder10	0.01	0.0312	1.01 [0.95, 1.07]
FOX2012 A ACR10-29	0.3221	0.0713	1.38 [1.20, 1.59]
FOX2012 A ACR30-299	0.6206	0.0642	1.86 [1.64, 2.11]
FOX2012 A ACRover300	0.8796	0.1267	2.41 [1.88, 3.09]
14.1.11 eGFR 75-89 with diabetes			
FOX2012 A ACRunder10	-0.0618754	0.03948372	0.94 [0.87, 1.02]
FOX2012 A ACR10-29	0.28517894	0.06977625	1.33 [1.16, 1.52]
FOX2012 A ACR30-299	0.46373402	0.08348593	1.59 [1.35, 1.87]
FOX2012 A ACRover300	0.88376754	0.12612003	2.42 [1.89, 3.10]
14.1.12 eGFR 75-89 without diabetes			
FOX2012 A ACRunder10	-0.0618754	0.02788746	0.94 [0.89, 0.99]
FOX2012 A ACR10-29	0.26236426	0.04941408	1.30 [1.18, 1.43]
FOX2012 A ACR30-299	0.47000363	0.06812951	1.60 [1.40, 1.83]
FOX2012 A ACRover300	0.9439059	0.13306829	2.57 [1.98, 3.34]
14.1.13 eGFR 90-104 with diabetes			
FOX2012 A ACRunder10	0	0	Not estimable
FOX2012 A ACR10-29	0.3435897	0.06555137	1.41 [1.24, 1.60]
FOX2012 A ACR30-299	0.54812141	0.09008219	1.73 [1.45, 2.06]
FOX2012 A ACRover300	1.08180517	0.14505265	2.95 [2.22, 3.92]
14.1.14 eGFR 90-104 without diabetes			
FOX2012 A ACRunder10	0	0	Not estimable
FOX2012 A ACR10-29	0.3852624	0.05491461	1.47 [1.32, 1.64]
FOX2012 A ACR30-299	0.5988365	0.05313376	1.82 [1.64, 2.02]
FOX2012 A ACRover300	1.17248214	0.15367056	3.23 [2.39, 4.37]
14.1.15 eGFR >105 with diabetes			
FOX2012 A ACRunder10	0.2390169	0.08742929	1.27 [1.07, 1.51]
FOX2012 A ACR10-29	0.45742485	0.10346243	1.58 [1.29, 1.94]
FOX2012 A ACR30-299	0.88789126	0.12553158	2.43 [1.90, 3.11]
FOX2012 A ACRover300	1.47704872	0.19821118	4.38 [2.97, 6.46]
14.1.16 eGFR >105 without diabetes			
FOX2012 A ACRunder10	0.2390169	0.05509726	1.27 [1.14, 1.41]
FOX2012 A ACR10-29	0.48242615	0.09302291	1.62 [1.35, 1.94]
FOX2012 A ACR30-299	0.87129337	0.08329621	2.39 [2.03, 2.81]
FOX2012 A ACRover300	1.68639895	0.24665078	5.40 [3.33, 8.76]



I.3.2.5 Subgroup - hypertension

Figure 56: All-cause mortality at varying ACR levels for those with and without hypertension

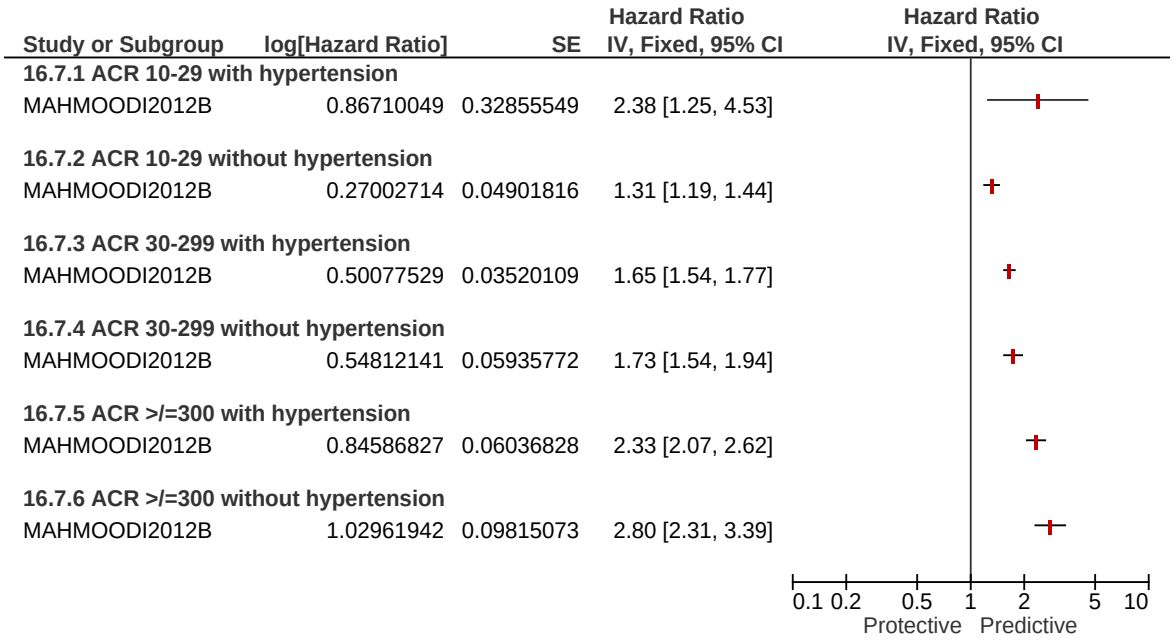
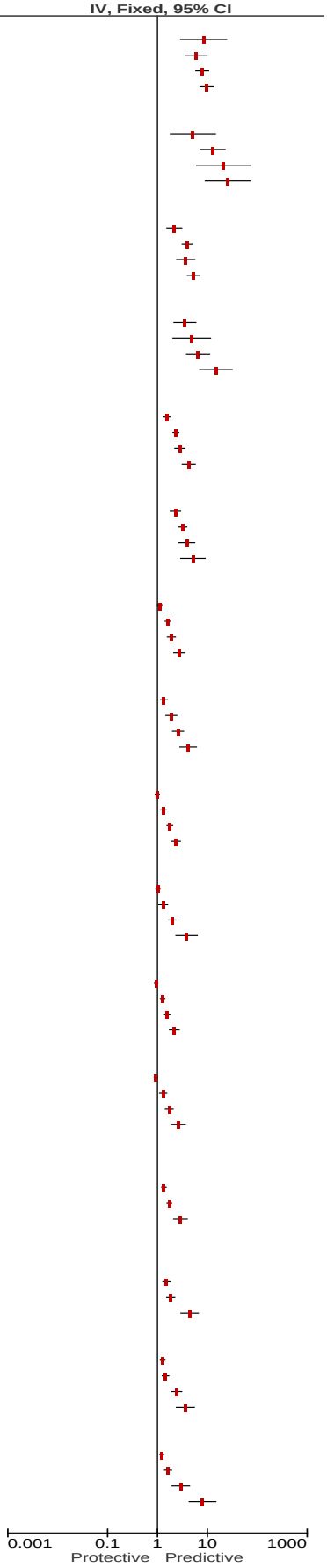


Figure 57: All-cause mortality stratified by eGFR for those with and without hypertension

Forest plots

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
17.1.1 eGFR <15 with hypertension			
MAHMOODI2012 B ACRunder10	2.1306	0.5368	8.42 [2.94, 24.11]
MAHMOODI2012 B ACR10-29	1.7884	0.2533	5.98 [3.64, 9.82]
MAHMOODI2012 B ACR 30-299	2.0656	0.1448	7.89 [5.94, 10.48]
MAHMOODI2012 B ACRover300	2.2762	0.1513	9.74 [7.24, 13.10]
17.1.2 eGFR <15 without hypertension			
MAHMOODI2012 B ACRunder10	1.6371	0.5269	5.14 [1.83, 14.44]
MAHMOODI2012 B ACR10-29	2.5494	0.2879	12.80 [7.28, 22.50]
MAHMOODI2012 B ACR 30-299	3.0493	0.6315	21.10 [6.12, 72.75]
MAHMOODI2012 B ACRover300	3.2465	0.5264	25.70 [9.16, 72.11]
17.1.3 eGFR 15-29 with hypertension			
MAHMOODI2012 B ACRunder10	0.7793	0.1707	2.18 [1.56, 3.05]
MAHMOODI2012 B ACR10-29	1.3712	0.1142	3.94 [3.15, 4.93]
MAHMOODI2012 B ACR 30-299	1.3083	0.2083	3.70 [2.46, 5.57]
MAHMOODI2012 B ACRover300	1.6601	0.1372	5.26 [4.02, 6.88]
17.1.4 eGFR 15-29 without hypertension			
MAHMOODI2012 B ACRunder10	1.2669	0.2535	3.55 [2.16, 5.83]
MAHMOODI2012 B ACR10-29	1.581	0.4379	4.86 [2.06, 11.46]
MAHMOODI2012 B ACR 30-299	1.8749	0.2675	6.52 [3.86, 11.01]
MAHMOODI2012 B ACRover300	2.6946	0.3769	14.80 [7.07, 30.98]
17.1.5 eGFR 30-44 with hypertension			
MAHMOODI2012 B ACRunder10	0.4253	0.0753	1.53 [1.32, 1.77]
MAHMOODI2012 B ACR10-29	0.8502	0.0626	2.34 [2.07, 2.65]
MAHMOODI2012 B ACR 30-299	1.0296	0.1116	2.80 [2.25, 3.48]
MAHMOODI2012 B ACRover300	1.4446	0.1484	4.24 [3.17, 5.67]
17.1.6 eGFR 30-44 without hypertension			
MAHMOODI2012 B ACRunder10	0.8286	0.1172	2.29 [1.82, 2.88]
MAHMOODI2012 B ACR10-29	1.1537	0.0972	3.17 [2.62, 3.84]
MAHMOODI2012 B ACR 30-299	1.3584	0.1807	3.89 [2.73, 5.54]
MAHMOODI2012 B ACRover300	1.639	0.2843	5.15 [2.95, 8.99]
17.1.7 eGFR 45-59 with hypertension			
MAHMOODI2012 B ACRunder10	0.1044	0.0482	1.11 [1.01, 1.22]
MAHMOODI2012 B ACR10-29	0.4824	0.0601	1.62 [1.44, 1.82]
MAHMOODI2012 B ACR 30-299	0.6419	0.0909	1.90 [1.59, 2.27]
MAHMOODI2012 B ACRover300	1.0006	0.1224	2.72 [2.14, 3.46]
17.1.8 eGFR 45-59 without hypertension			
MAHMOODI2012 B ACRunder10	0.3001	0.0774	1.35 [1.16, 1.57]
MAHMOODI2012 B ACR10-29	0.6419	0.124	1.90 [1.49, 2.42]
MAHMOODI2012 B ACR 30-299	0.9517	0.1268	2.59 [2.02, 3.32]
MAHMOODI2012 B ACRover300	1.4159	0.1916	4.12 [2.83, 6.00]
17.1.9 eGFR 60-74 with hypertension			
MAHMOODI2012 B ACRunder10	-0.0101	0.043	0.99 [0.91, 1.08]
MAHMOODI2012 B ACR10-29	0.27	0.0665	1.31 [1.15, 1.49]
MAHMOODI2012 B ACR 30-299	0.571	0.0612	1.77 [1.57, 2.00]
MAHMOODI2012 B ACRover300	0.8416	0.1046	2.32 [1.89, 2.85]
17.1.10 eGFR 60-74 without hypertension			
MAHMOODI2012 B ACRunder10	0.0198	0.0417	1.02 [0.94, 1.11]
MAHMOODI2012 B ACR10-29	0.2624	0.0993	1.30 [1.07, 1.58]
MAHMOODI2012 B ACR 30-299	0.6678	0.0852	1.95 [1.65, 2.30]
MAHMOODI2012 B ACRover300	1.3455	0.2462	3.84 [2.37, 6.22]
17.1.11 eGFR 75-89 with hypertension			
MAHMOODI2012 B ACRunder10	-0.0618754	0.03365264	0.94 [0.88, 1.00]
MAHMOODI2012 B ACR10-29	0.2390169	0.04622376	1.27 [1.16, 1.39]
MAHMOODI2012 B ACR 30-299	0.45742485	0.06171165	1.58 [1.40, 1.78]
MAHMOODI2012 B ACRover300	0.77932488	0.10919133	2.18 [1.76, 2.70]
17.1.12 eGFR 75-89 without hypertension			
MAHMOODI2012 B ACRunder10	-0.07257069	0.03402684	0.93 [0.87, 0.99]
MAHMOODI2012 B ACR10-29	0.26236426	0.08061589	1.30 [1.11, 1.52]
MAHMOODI2012 B ACR 30-299	0.54232429	0.08712442	1.72 [1.45, 2.04]
MAHMOODI2012 B ACRover300	0.95935022	0.1619909	2.61 [1.90, 3.59]
17.1.13 eGFR 90-104 with hypertension			
MAHMOODI2012 B ACRunder10	0	0	Not estimable
MAHMOODI2012 B ACR10-29	0.30010459	0.04749599	1.35 [1.23, 1.48]
MAHMOODI2012 B ACR 30-299	0.54812141	0.04951407	1.73 [1.57, 1.91]
MAHMOODI2012 B ACRover300	1.0612565	0.15568374	2.89 [2.13, 3.92]
17.1.14 eGFR 90-104 without hypertension			
MAHMOODI2012 B ACRunder10	0	0	Not estimable
MAHMOODI2012 B ACR10-29	0.41871033	0.07976987	1.52 [1.30, 1.78]
MAHMOODI2012 B ACR 30-299	0.60976557	0.0908094	1.84 [1.54, 2.20]
MAHMOODI2012 B ACRover300	1.48387469	0.20169388	4.41 [2.97, 6.55]
17.1.15 eGFR >105 with hypertension			
MAHMOODI2012 B ACRunder10	0.2390169	0.05064122	1.27 [1.15, 1.40]
MAHMOODI2012 B ACR10-29	0.37156356	0.07166042	1.45 [1.26, 1.67]
MAHMOODI2012 B ACR 30-299	0.87546874	0.11919344	2.40 [1.90, 3.03]
MAHMOODI2012 B ACRover300	1.28647403	0.20546627	3.62 [2.42, 5.42]
17.1.16 eGFR >105 without hypertension			
MAHMOODI2012 B ACRunder10	0.19885086	0.04363456	1.22 [1.12, 1.33]
MAHMOODI2012 B ACR10-29	0.48858001	0.07760744	1.63 [1.40, 1.90]
MAHMOODI2012 B ACR 30-299	1.07840958	0.20169388	2.94 [1.98, 4.37]
MAHMOODI2012 B ACRover300	2.07944154	0.309684	8.00 [4.36, 14.68]



I.3.3 Cardiovascular mortality

Figure 58: Cardiovascular mortality and different ACR levels

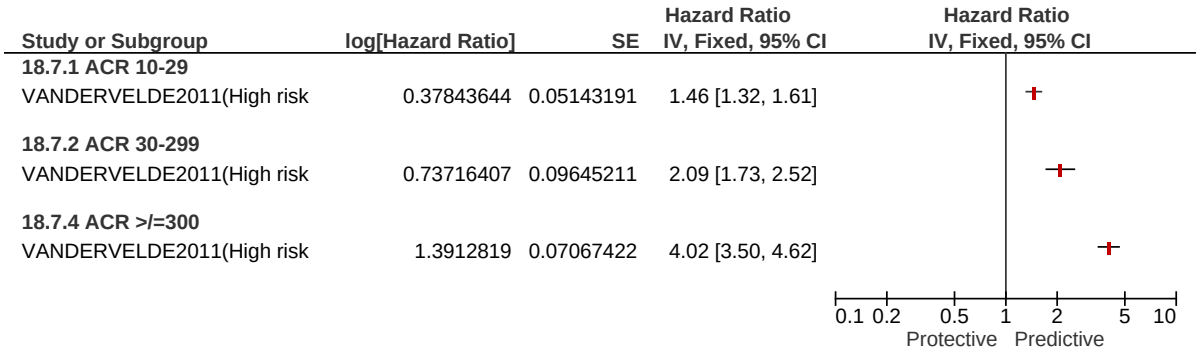
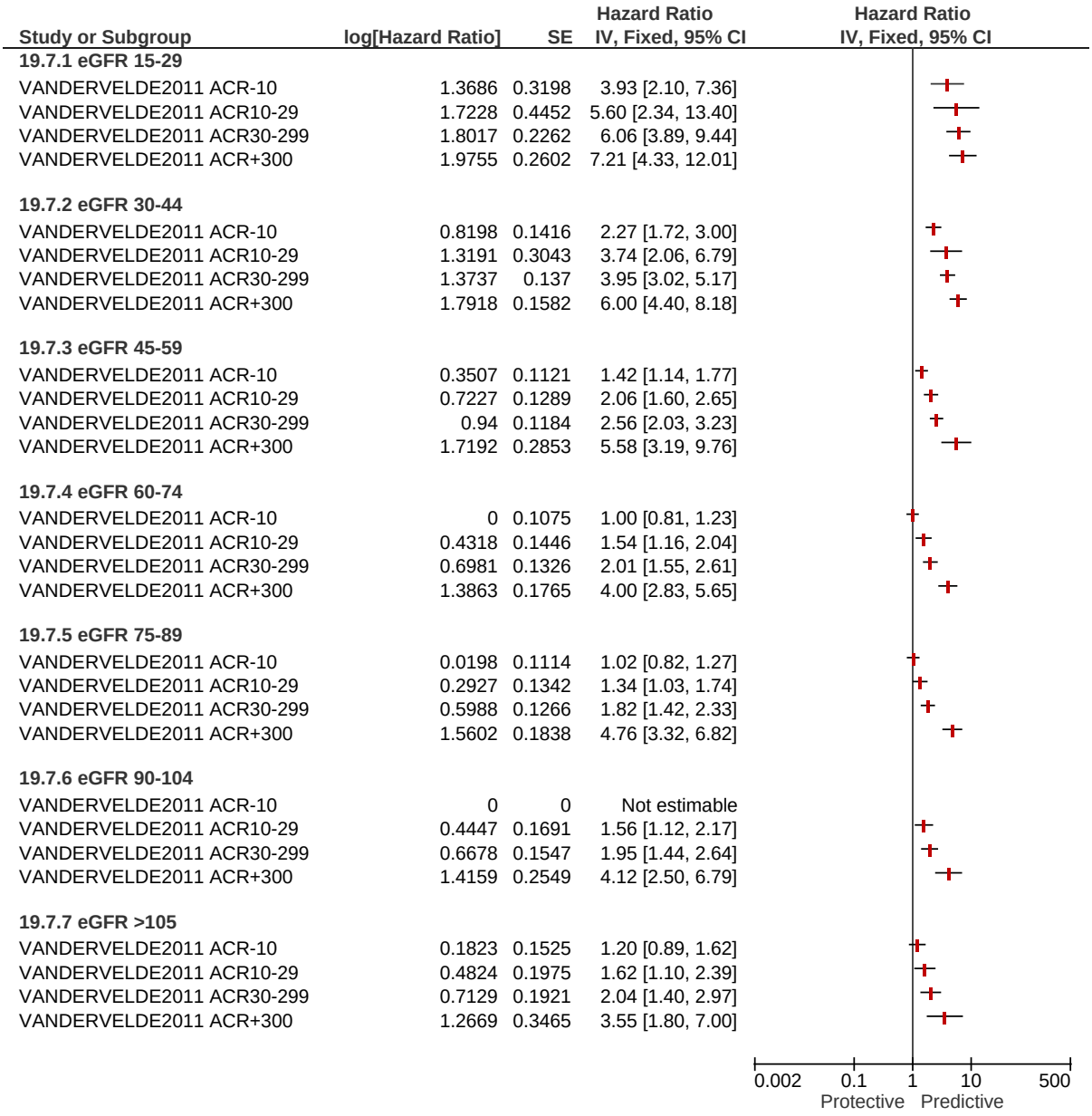


Figure 59: Cardiovascular mortality stratified by eGFR



I.3.3.1 Subgroup – age

Figure 60: Cardiovascular mortality at varying ACR levels for those <65 years and >65 years

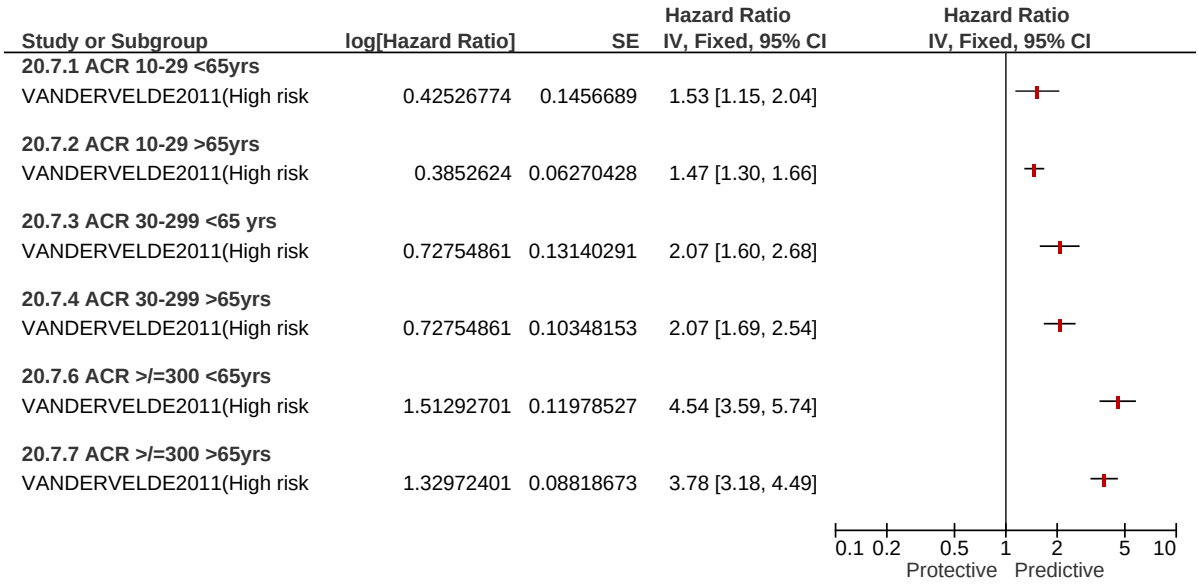
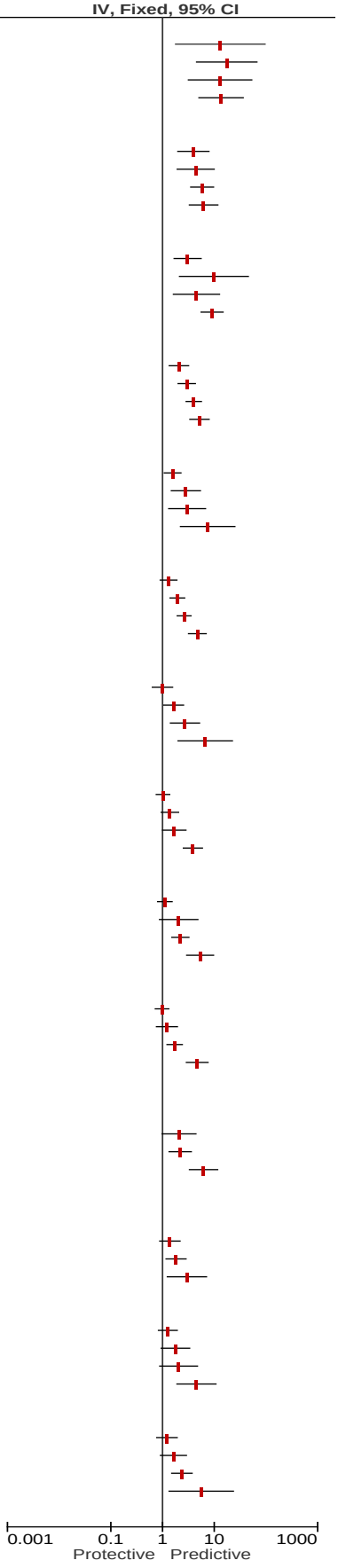


Figure 61: Cardiovascular mortality stratified by eGFR for those <65 years and >65 years

Forest plots

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
19.1.1 eGFR 15-29 <65yrs			
VANDERVELDE2011 ACR-10	2.5741	1.0135	13.12 [1.80, 95.63]
VANDERVELDE2011 ACR10-29	2.8633	0.6834	17.52 [4.59, 66.87]
VANDERVELDE2011 ACR30-299	2.5649	0.7168	13.00 [3.19, 52.97]
VANDERVELDE2011 ACR+300	2.6101	0.4994	13.60 [5.11, 36.19]
19.1.2 eGFR 15-29 >65yrs			
VANDERVELDE2011 ACR-10	1.3762	0.3511	3.96 [1.99, 7.88]
VANDERVELDE2011 ACR10-29	1.4793	0.4167	4.39 [1.94, 9.93]
VANDERVELDE2011 ACR30-299	1.7664	0.2577	5.85 [3.53, 9.69]
VANDERVELDE2011 ACR+300	1.831	0.3204	6.24 [3.33, 11.69]
19.1.3 eGFR 30-44 <65yrs			
VANDERVELDE2011 ACR-10	1.1184	0.3029	3.06 [1.69, 5.54]
VANDERVELDE2011 ACR10-29	2.2915	0.7786	9.89 [2.15, 45.49]
VANDERVELDE2011 ACR30-299	1.5151	0.5206	4.55 [1.64, 12.62]
VANDERVELDE2011 ACR+300	2.2105	0.2461	9.12 [5.63, 14.77]
19.1.4 eGFR 30-44 >65yrs			
VANDERVELDE2011 ACR-10	0.7324	0.2168	2.08 [1.36, 3.18]
VANDERVELDE2011 ACR10-29	1.0818	0.1932	2.95 [2.02, 4.31]
VANDERVELDE2011 ACR30-299	1.3938	0.1697	4.03 [2.89, 5.62]
VANDERVELDE2011 ACR+300	1.6487	0.2153	5.20 [3.41, 7.93]
19.1.5 eGFR 45-59 <65yrs			
VANDERVELDE2011 ACR-10	0.4511	0.1862	1.57 [1.09, 2.26]
VANDERVELDE2011 ACR10-29	1.0403	0.3273	2.83 [1.49, 5.38]
VANDERVELDE2011 ACR30-299	1.0986	0.415	3.00 [1.33, 6.77]
VANDERVELDE2011 ACR+300	2.0122	0.6152	7.48 [2.24, 24.98]
19.1.6 eGFR 45-59 >65yrs			
VANDERVELDE2011 ACR-10	0.27	0.1859	1.31 [0.91, 1.89]
VANDERVELDE2011 ACR10-29	0.6627	0.1628	1.94 [1.41, 2.67]
VANDERVELDE2011 ACR30-299	0.9632	0.1533	2.62 [1.94, 3.54]
VANDERVELDE2011 ACR+300	1.5539	0.1978	4.73 [3.21, 6.97]
19.1.7 eGFR 60-74 <65yrs			
VANDERVELDE2011 ACR-10	0	0.2277	1.00 [0.64, 1.56]
VANDERVELDE2011 ACR10-29	0.5008	0.221	1.65 [1.07, 2.54]
VANDERVELDE2011 ACR30-299	1.0006	0.328	2.72 [1.43, 5.17]
VANDERVELDE2011 ACR+300	1.9036	0.615	6.71 [2.01, 22.40]
19.1.8 eGFR 60-74 >65yrs			
VANDERVELDE2011 ACR-10	0.0198	0.1501	1.02 [0.76, 1.37]
VANDERVELDE2011 ACR10-29	0.3293	0.1942	1.39 [0.95, 2.03]
VANDERVELDE2011 ACR30-299	0.5247	0.2626	1.69 [1.01, 2.83]
VANDERVELDE2011 ACR+300	1.3533	0.2128	3.87 [2.55, 5.87]
19.1.9 eGFR 75-89 <65yrs			
VANDERVELDE2011 ACR-10	0.1044	0.1608	1.11 [0.81, 1.52]
VANDERVELDE2011 ACR10-29	0.7227	0.434	2.06 [0.88, 4.82]
VANDERVELDE2011 ACR30-299	0.7975	0.1899	2.22 [1.53, 3.22]
VANDERVELDE2011 ACR+300	1.6771	0.302	5.35 [2.96, 9.67]
19.1.10 eGFR 75-89 >65yrs			
VANDERVELDE2011 ACR-10	-0.0202	0.1503	0.98 [0.73, 1.32]
VANDERVELDE2011 ACR10-29	0.1989	0.2348	1.22 [0.77, 1.93]
VANDERVELDE2011 ACR30-299	0.5423	0.1711	1.72 [1.23, 2.41]
VANDERVELDE2011 ACR+300	1.5476	0.2429	4.70 [2.92, 7.57]
19.1.11 eGFR 90-104 <65 yrs			
VANDERVELDE2011 ACR-10	0	0	Not estimable
VANDERVELDE2011 ACR10-29	0.7372	0.3812	2.09 [0.99, 4.41]
VANDERVELDE2011 ACR30-299	0.7885	0.2492	2.20 [1.35, 3.59]
VANDERVELDE2011 ACR+300	1.831	0.3174	6.24 [3.35, 11.62]
19.1.12 eGFR 90-104 >65yrs			
VANDERVELDE2011 ACR-10	0	0	Not estimable
VANDERVELDE2011 ACR10-29	0.3293	0.2275	1.39 [0.89, 2.17]
VANDERVELDE2011 ACR30-299	0.6043	0.2239	1.83 [1.18, 2.84]
VANDERVELDE2011 ACR+300	1.0886	0.4415	2.97 [1.25, 7.06]
19.1.13 eGFR >105 <65yrs			
VANDERVELDE2011 ACR-10	0.239	0.2109	1.27 [0.84, 1.92]
VANDERVELDE2011 ACR10-29	0.5766	0.3204	1.78 [0.95, 3.34]
VANDERVELDE2011 ACR30-299	0.7178	0.4257	2.05 [0.89, 4.72]
VANDERVELDE2011 ACR+300	1.5151	0.4402	4.55 [1.92, 10.78]
19.1.14 eGFR >105 >65yrs			
VANDERVELDE2011 ACR-10	0.1989	0.2282	1.22 [0.78, 1.91]
VANDERVELDE2011 ACR10-29	0.4886	0.2918	1.63 [0.92, 2.89]
VANDERVELDE2011 ACR30-299	0.8671	0.2288	2.38 [1.52, 3.73]
VANDERVELDE2011 ACR+300	1.7263	0.7277	5.62 [1.35, 23.40]



I.3.3.2 Subgroup – diabetes

Figure 62: Cardiovascular mortality at varying ACR levels for those with and without diabetes

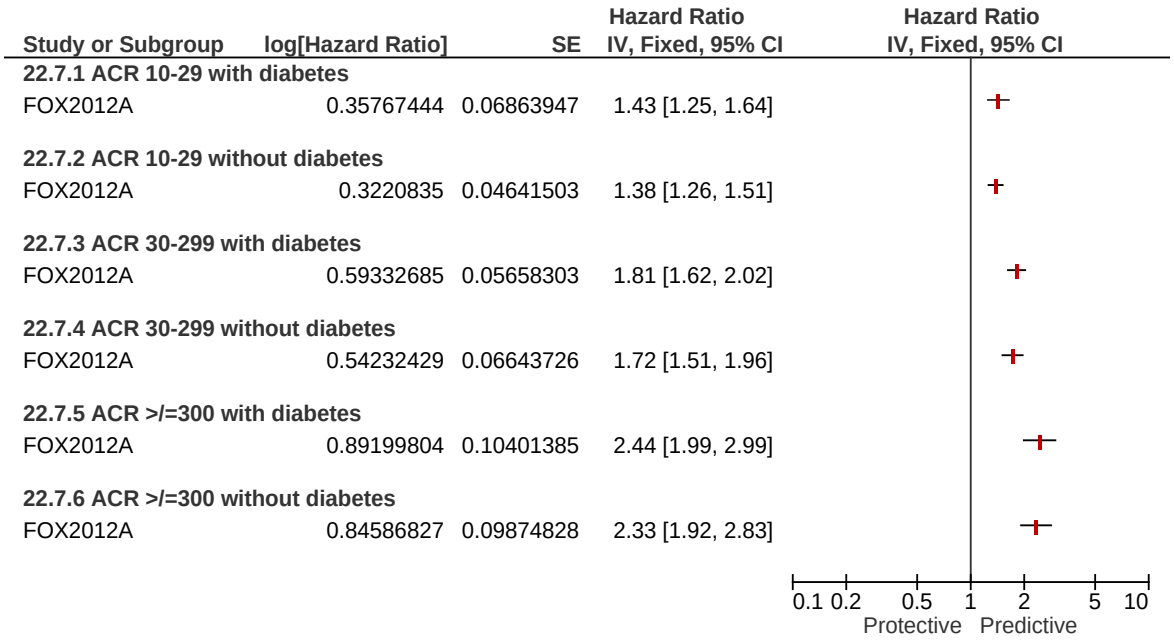
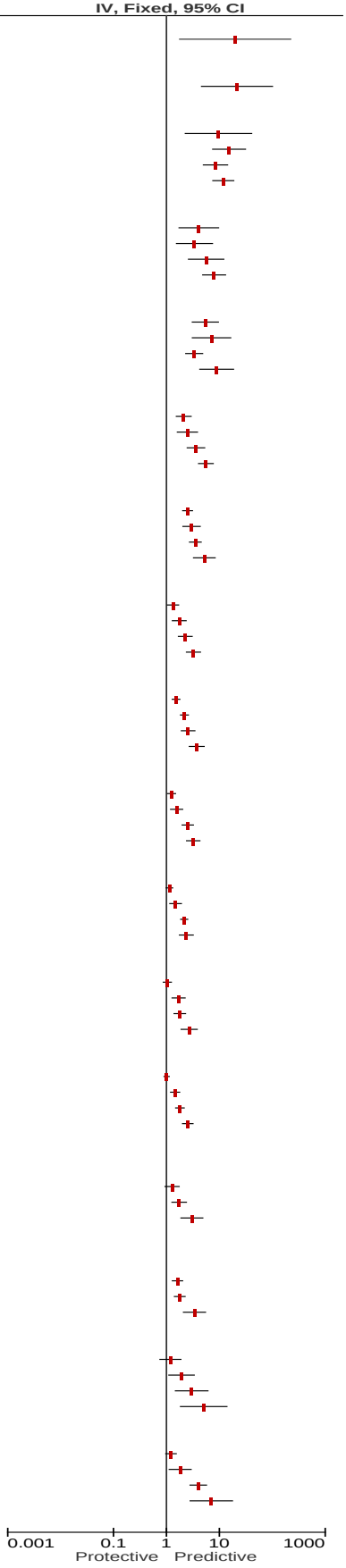


Figure 63: Cardiovascular mortality stratified by eGFR for those with and without diabetes

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
21.1.1 eGFR <15 with diabetes			
FOX2012 A ACRunder10	2.9907	1.2289	19.90 [1.79, 221.25]
FOX2012 A ACR10-29	0	0	Not estimable
FOX2012 A ACR30-299	0	0	Not estimable
FOX2012 A ACRover300	3.0727	0.7836	21.60 [4.65, 100.34]
21.1.2 eGFR <15 without diabetes			
FOX2012 A ACRunder10	2.2649	0.7328	9.63 [2.29, 40.49]
FOX2012 A ACR10-29	2.7279	0.3597	15.30 [7.56, 30.97]
FOX2012 A ACR30-299	2.1353	0.2643	8.46 [5.04, 14.20]
FOX2012 A ACRover300	2.4765	0.2274	11.90 [7.62, 18.58]
21.1.3 eGFR 15-29 with diabetes			
FOX2012 A ACRunder10	1.411	0.4344	4.10 [1.75, 9.61]
FOX2012 A ACR10-29	1.2208	0.396	3.39 [1.56, 7.37]
FOX2012 A ACR30-299	1.7299	0.3873	5.64 [2.64, 12.05]
FOX2012 A ACRover300	2.0744	0.2486	7.96 [4.89, 12.96]
21.1.4 eGFR 15-29 without diabetes			
FOX2012 A ACRunder10	1.6938	0.2853	5.44 [3.11, 9.52]
FOX2012 A ACR10-29	1.9629	0.421	7.12 [3.12, 16.25]
FOX2012 A ACR30-299	1.209	0.1831	3.35 [2.34, 4.80]
FOX2012 A ACRover300	2.1872	0.3705	8.91 [4.31, 18.42]
21.1.5 eGFR 30-44 with diabetes			
FOX2012 A ACRunder10	0.7514	0.1598	2.12 [1.55, 2.90]
FOX2012 A ACR10-29	0.9123	0.2193	2.49 [1.62, 3.83]
FOX2012 A ACR30-299	1.2865	0.1889	3.62 [2.50, 5.24]
FOX2012 A ACRover300	1.7174	0.1588	5.57 [4.08, 7.60]
21.1.6 eGFR 30-44 without diabetes			
FOX2012 A ACRunder10	0.9203	0.1033	2.51 [2.05, 3.07]
FOX2012 A ACR10-29	1.0953	0.1876	2.99 [2.07, 4.32]
FOX2012 A ACR30-299	1.2585	0.1241	3.52 [2.76, 4.49]
FOX2012 A ACRover300	1.6506	0.2361	5.21 [3.28, 8.28]
21.1.7 eGFR 45-59 with diabetes			
FOX2012 A ACRunder10	0.2852	0.1206	1.33 [1.05, 1.68]
FOX2012 A ACR10-29	0.5596	0.1478	1.75 [1.31, 2.34]
FOX2012 A ACR30-299	0.8198	0.1475	2.27 [1.70, 3.03]
FOX2012 A ACRover300	1.1756	0.151	3.24 [2.41, 4.36]
21.1.8 eGFR 45-59 without diabetes			
FOX2012 A ACRunder10	0.4187	0.0798	1.52 [1.30, 1.78]
FOX2012 A ACR10-29	0.7839	0.0833	2.19 [1.86, 2.58]
FOX2012 A ACR30-299	0.9439	0.1461	2.57 [1.93, 3.42]
FOX2012 A ACRover300	1.3191	0.1606	3.74 [2.73, 5.12]
21.1.9 eGFR 60-74 with diabetes			
FOX2012 A ACRunder10	0.2231	0.0841	1.25 [1.06, 1.47]
FOX2012 A ACR10-29	0.4447	0.1296	1.56 [1.21, 2.01]
FOX2012 A ACR30-299	0.9282	0.1199	2.53 [2.00, 3.20]
FOX2012 A ACRover300	1.1663	0.1441	3.21 [2.42, 4.26]
21.1.10 eGFR 60-74 without diabetes			
FOX2012 A ACRunder10	0.131	0.0669	1.14 [1.00, 1.30]
FOX2012 A ACR10-29	0.3988	0.1234	1.49 [1.17, 1.90]
FOX2012 A ACR30-299	0.7747	0.0732	2.17 [1.88, 2.50]
FOX2012 A ACRover300	0.8671	0.1482	2.38 [1.78, 3.18]
21.1.11 eGFR 75-89 with diabetes			
FOX2012 A ACRunder10	0.03922071	0.08523324	1.04 [0.88, 1.23]
FOX2012 A ACR10-29	0.53062825	0.14081179	1.70 [1.29, 2.24]
FOX2012 A ACR30-299	0.58221562	0.12175015	1.79 [1.41, 2.27]
FOX2012 A ACRover300	0.98954119	0.17471645	2.69 [1.91, 3.79]
21.1.12 eGFR 75-89 without diabetes			
FOX2012 A ACRunder10	0.00995033	0.05319537	1.01 [0.91, 1.12]
FOX2012 A ACR10-29	0.37843644	0.09582629	1.46 [1.21, 1.76]
FOX2012 A ACR30-299	0.58778666	0.08963278	1.80 [1.51, 2.15]
FOX2012 A ACRover300	0.9282193	0.11234059	2.53 [2.03, 3.15]
21.1.13 eGFR 90-104 with diabetes			
FOX2012 A ACRunder10	0	0	Not estimable
FOX2012 A ACR10-29	0.24686008	0.15212186	1.28 [0.95, 1.72]
FOX2012 A ACR30-299	0.55388511	0.1566483	1.74 [1.28, 2.37]
FOX2012 A ACRover300	1.10856262	0.23812108	3.03 [1.90, 4.83]
21.1.14 eGFR 90-104 without diabetes			
FOX2012 A ACRunder10	0	0	Not estimable
FOX2012 A ACR10-29	0.48242615	0.10836883	1.62 [1.31, 2.00]
FOX2012 A ACR30-299	0.58221562	0.11456393	1.79 [1.43, 2.24]
FOX2012 A ACRover300	1.22082992	0.23950125	3.39 [2.12, 5.42]
21.1.15 eGFR >105 with diabetes			
FOX2012 A ACRunder10	0.17395331	0.22877469	1.19 [0.76, 1.86]
FOX2012 A ACR10-29	0.65752	0.27765373	1.93 [1.12, 3.33]
FOX2012 A ACR30-299	1.09861229	0.35706583	3.00 [1.49, 6.04]
FOX2012 A ACRover300	1.62334082	0.51162386	5.07 [1.86, 13.82]
21.1.16 eGFR >105 without diabetes			
FOX2012 A ACRunder10	0.19885086	0.11176408	1.22 [0.98, 1.52]
FOX2012 A ACR10-29	0.5988365	0.23868206	1.82 [1.14, 2.91]
FOX2012 A ACR30-299	1.38629436	0.17834893	4.00 [2.82, 5.67]
FOX2012 A ACRover300	1.95160817	0.46497357	7.04 [2.83, 17.51]



I.3.3.3 Subgroup – hypertension

Figure 64: Cardiovascular mortality at varying ACR levels for those with and without hypertension

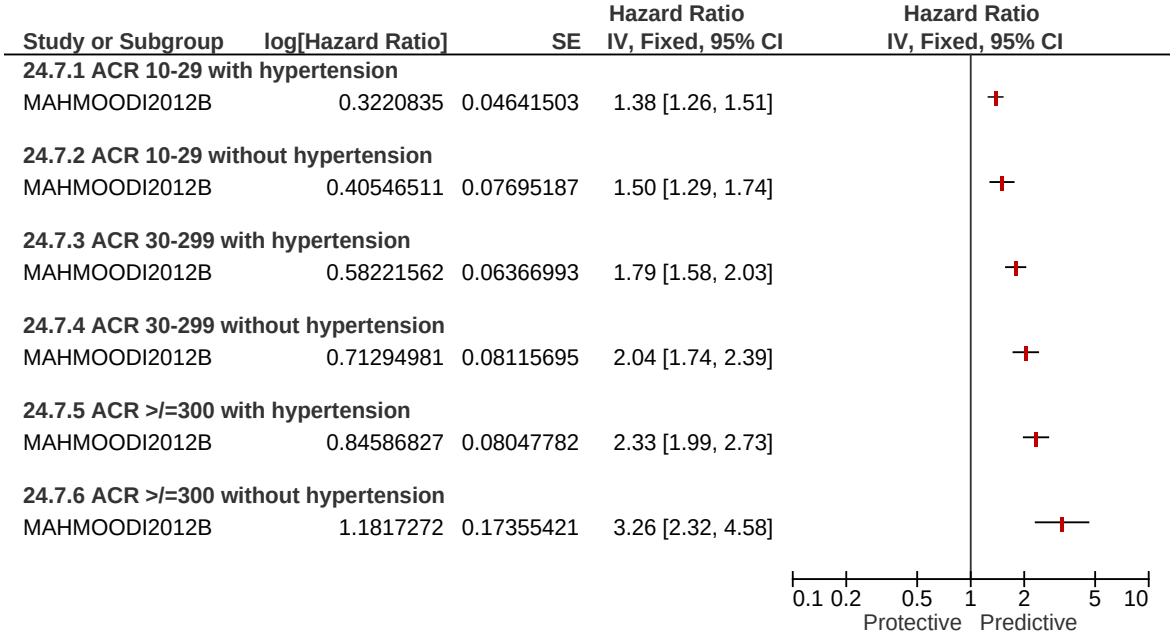
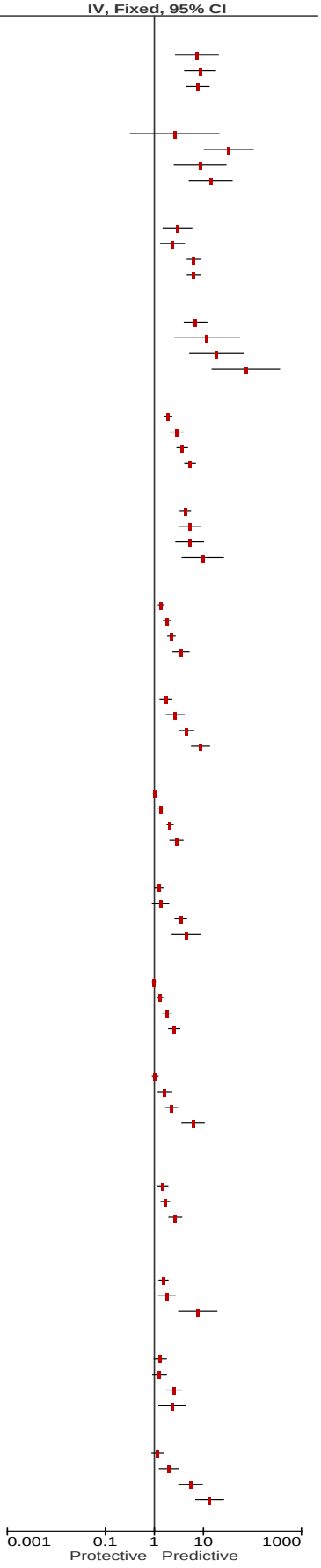


Figure 65: Cardiovascular mortality stratified by eGFR for those with and without hypertension

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
25.1.1 eGFR <15 with hypertension			
MAHMOODI2012 B ACRunder10	0	0	Not estimable
MAHMOODI2012 B ACR10-29	2.0015	0.5069	7.40 [2.74, 19.99]
MAHMOODI2012 B ACR 30-299	2.1483	0.3639	8.57 [4.20, 17.49]
MAHMOODI2012 B ACRover300	2.0477	0.2628	7.75 [4.63, 12.97]
25.1.2 eGFR <15 without hypertension			
MAHMOODI2012 B ACRunder10	0.9555	1.0532	2.60 [0.33, 20.49]
MAHMOODI2012 B ACR10-29	3.4965	0.5843	33.00 [10.50, 103.72]
MAHMOODI2012 B ACR 30-299	2.1506	0.6157	8.59 [2.57, 28.71]
MAHMOODI2012 B ACRover300	2.6462	0.5089	14.10 [5.20, 38.23]
25.1.3 eGFR 15-29 with hypertension			
MAHMOODI2012 B ACRunder10	1.0852	0.34	2.96 [1.52, 5.76]
MAHMOODI2012 B ACR10-29	0.8544	0.2828	2.35 [1.35, 4.09]
MAHMOODI2012 B ACR 30-299	1.8532	0.1527	6.38 [4.73, 8.61]
MAHMOODI2012 B ACRover300	1.8532	0.1527	6.38 [4.73, 8.61]
25.1.4 eGFR 15-29 without hypertension			
MAHMOODI2012 B ACRunder10	1.9373	0.2661	6.94 [4.12, 11.69]
MAHMOODI2012 B ACR10-29	2.4765	0.7702	11.90 [2.63, 53.84]
MAHMOODI2012 B ACR 30-299	2.9285	0.6404	18.70 [5.33, 65.61]
MAHMOODI2012 B ACRover300	4.2986	0.8048	73.60 [15.20, 356.37]
25.1.5 eGFR 30-44 with hypertension			
MAHMOODI2012 B ACRunder10	0.6575	0.0769	1.93 [1.66, 2.24]
MAHMOODI2012 B ACR10-29	1.0473	0.1558	2.85 [2.10, 3.87]
MAHMOODI2012 B ACR 30-299	1.3083	0.1208	3.70 [2.92, 4.69]
MAHMOODI2012 B ACRover300	1.679	0.1232	5.36 [4.21, 6.82]
25.1.6 eGFR 30-44 without hypertension			
MAHMOODI2012 B ACRunder10	1.4563	0.1201	4.29 [3.39, 5.43]
MAHMOODI2012 B ACR10-29	1.6696	0.2458	5.31 [3.28, 8.60]
MAHMOODI2012 B ACR 30-299	1.6601	0.3272	5.26 [2.77, 9.99]
MAHMOODI2012 B ACRover300	2.2762	0.4884	9.74 [3.74, 25.37]
25.1.7 eGFR 45-59 with hypertension			
MAHMOODI2012 B ACRunder10	0.3001	0.0517	1.35 [1.22, 1.49]
MAHMOODI2012 B ACR10-29	0.5933	0.0824	1.81 [1.54, 2.13]
MAHMOODI2012 B ACR 30-299	0.802	0.0844	2.23 [1.89, 2.63]
MAHMOODI2012 B ACRover300	1.2528	0.1883	3.50 [2.42, 5.06]
25.1.8 eGFR 45-59 without hypertension			
MAHMOODI2012 B ACRunder10	0.5423	0.135	1.72 [1.32, 2.24]
MAHMOODI2012 B ACR10-29	0.9746	0.2117	2.65 [1.75, 4.01]
MAHMOODI2012 B ACR 30-299	1.5195	0.1661	4.57 [3.30, 6.33]
MAHMOODI2012 B ACRover300	2.1691	0.2107	8.75 [5.79, 13.22]
25.1.9 eGFR 60-74 with hypertension			
MAHMOODI2012 B ACRunder10	0.0296	0.0359	1.03 [0.96, 1.11]
MAHMOODI2012 B ACR10-29	0.3148	0.0676	1.37 [1.20, 1.56]
MAHMOODI2012 B ACR 30-299	0.7419	0.0702	2.10 [1.83, 2.41]
MAHMOODI2012 B ACRover300	1.0403	0.1522	2.83 [2.10, 3.81]
25.1.10 eGFR 60-74 without hypertension			
MAHMOODI2012 B ACRunder10	0.207	0.0955	1.23 [1.02, 1.48]
MAHMOODI2012 B ACR10-29	0.2927	0.1919	1.34 [0.92, 1.95]
MAHMOODI2012 B ACR 30-299	1.2442	0.1337	3.47 [2.67, 4.51]
MAHMOODI2012 B ACRover300	1.4974	0.3324	4.47 [2.33, 8.58]
25.1.11 eGFR 75-89 with hypertension			
MAHMOODI2012 B ACRunder10	-0.02020271	0.03223473	0.98 [0.92, 1.04]
MAHMOODI2012 B ACR10-29	0.25464222	0.0630695	1.29 [1.14, 1.46]
MAHMOODI2012 B ACR 30-299	0.60431597	0.10145638	1.83 [1.50, 2.23]
MAHMOODI2012 B ACRover300	0.93216408	0.12707746	2.54 [1.98, 3.26]
25.1.12 eGFR 75-89 without hypertension			
MAHMOODI2012 B ACRunder10	0.03922071	0.06255335	1.04 [0.92, 1.18]
MAHMOODI2012 B ACR10-29	0.49469624	0.15937777	1.64 [1.20, 2.24]
MAHMOODI2012 B ACR 30-299	0.81093022	0.13704636	2.25 [1.72, 2.94]
MAHMOODI2012 B ACRover300	1.81969884	0.26367122	6.17 [3.68, 10.34]
25.1.13 eGFR 90-104 with hypertension			
MAHMOODI2012 B ACRunder10	0	0	Not estimable
MAHMOODI2012 B ACR10-29	0.39204209	0.11991972	1.48 [1.17, 1.87]
MAHMOODI2012 B ACR 30-299	0.51282363	0.09731818	1.67 [1.38, 2.02]
MAHMOODI2012 B ACRover300	0.98581679	0.14932398	2.68 [2.00, 3.59]
25.1.14 eGFR 90-104 without hypertension			
MAHMOODI2012 B ACRunder10	0	0	Not estimable
MAHMOODI2012 B ACR10-29	0.43178242	0.10238489	1.54 [1.26, 1.88]
MAHMOODI2012 B ACR 30-299	0.58778666	0.19427525	1.80 [1.23, 2.63]
MAHMOODI2012 B ACRover300	2.04122033	0.4528087	7.70 [3.17, 18.70]
25.1.15 eGFR >105 with hypertension			
MAHMOODI2012 B ACRunder10	0.27763174	0.14165145	1.32 [1.00, 1.74]
MAHMOODI2012 B ACR10-29	0.24686008	0.157521	1.28 [0.94, 1.74]
MAHMOODI2012 B ACR 30-299	0.94000726	0.17406991	2.56 [1.82, 3.60]
MAHMOODI2012 B ACRover300	0.85015093	0.3199076	2.34 [1.25, 4.38]
25.1.16 eGFR >105 without hypertension			
MAHMOODI2012 B ACRunder10	0.14842001	0.12948224	1.16 [0.90, 1.50]
MAHMOODI2012 B ACR10-29	0.68813464	0.22514422	1.99 [1.28, 3.09]
MAHMOODI2012 B ACR 30-299	1.69927862	0.27673846	5.47 [3.18, 9.41]
MAHMOODI2012 B ACRover300	2.59525471	0.3276729	13.40 [7.05, 25.47]



I.3.4 Acute kidney injury

Figure 66: Occurrence of acute kidney injury at different ACR levels

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
26.7.2 ACR 30-299			
GANSEVOORT2011(High risk)	0.99325177	0.10448887	2.70 [2.20, 3.31]
26.7.4 ACR >/=300			
GANSEVOORT2011(High risk)	2.00148	0.15139661	7.40 [5.50, 9.96]

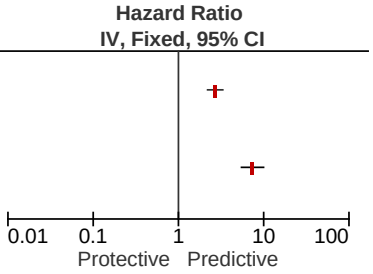
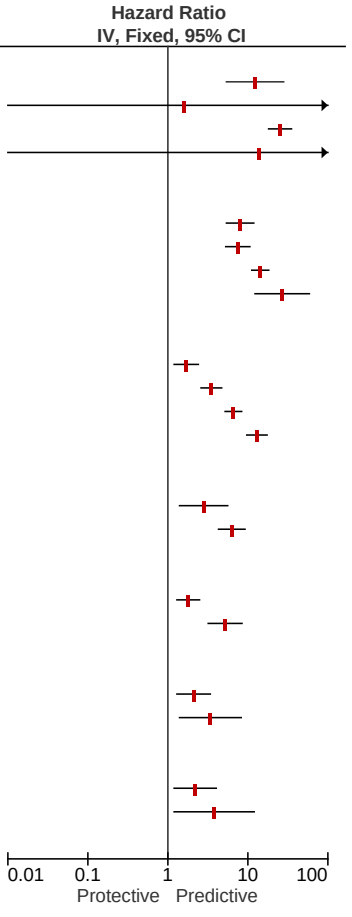


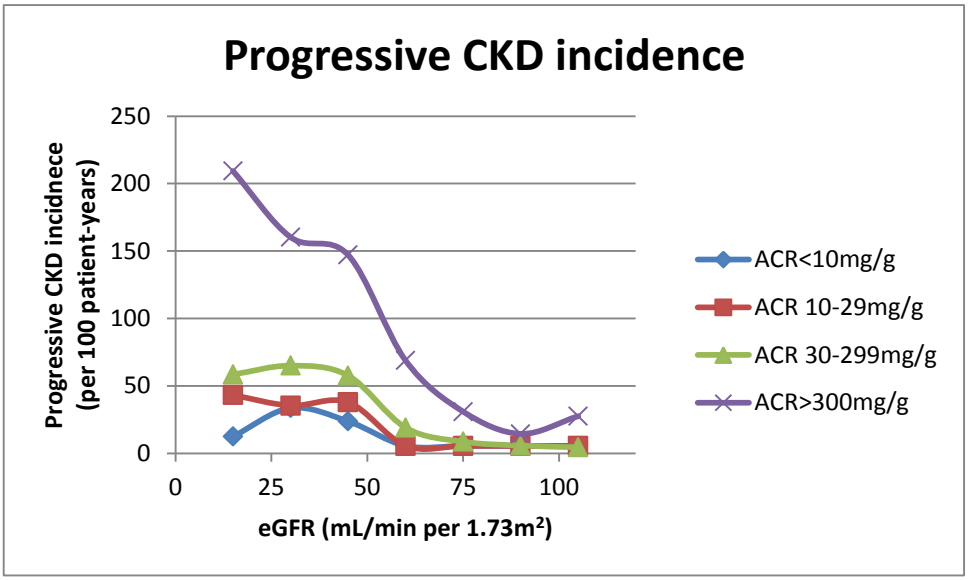
Figure 67: Occurrence of acute kidney injury stratified by eGFR

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
26.1.1 eGFR 15-29			
GANSEVOORT2011 ACRunder10	2.50959926	0.42000788	12.30 [5.40, 28.02]
GANSEVOORT2011 ACR10-29	0.47000363	∞	1.60 [0.00, Not estimable]
GANSEVOORT2011 ACR30-299	3.2308044	0.16805554	25.30 [18.20, 35.17]
GANSEVOORT2011 ACRover300	2.61739583	∞	13.70 [0.00, Not estimable]
26.1.2 eGFR 30-44			
GANSEVOORT2011 ACRunder10	2.07944154	0.20053562	8.00 [5.40, 11.85]
GANSEVOORT2011 ACR10-29	2.01490302	0.17714417	7.50 [5.30, 10.61]
GANSEVOORT2011 ACR30-299	2.66025954	0.12466849	14.30 [11.20, 18.26]
GANSEVOORT2011 ACRover300	3.29212629	0.39925582	26.90 [12.30, 58.83]
26.1.3 eGFR 45-59			
GANSEVOORT2011 ACRunder10	0.53062825	0.17771076	1.70 [1.20, 2.41]
GANSEVOORT2011 ACR10-29	1.25276297	0.15166173	3.50 [2.60, 4.71]
GANSEVOORT2011 ACR30-299	1.88706965	0.12164051	6.60 [5.20, 8.38]
GANSEVOORT2011 ACRover300	2.56494936	0.14940248	13.00 [9.70, 17.42]
26.1.4 eGFR 60-74			
GANSEVOORT2011 ACR30-299	1.02961942	0.35365302	2.80 [1.40, 5.60]
GANSEVOORT2011 ACRover300	1.84054963	0.19486818	6.30 [4.30, 9.23]
26.1.5 eGFR 75-89			
GANSEVOORT2011 ACR30-299	0.58778666	0.16603489	1.80 [1.30, 2.49]
GANSEVOORT2011 ACRover300	1.64865863	0.24771262	5.20 [3.20, 8.45]
26.1.6 eGFR 90-104			
GANSEVOORT2011 ACR30-299	0.74193734	0.24468464	2.10 [1.30, 3.39]
GANSEVOORT2011 ACRover300	1.22377543	0.45271403	3.40 [1.40, 8.26]
26.1.7 eGFR>105			
GANSEVOORT2011 ACR30-299	0.78845736	0.30925864	2.20 [1.20, 4.03]
GANSEVOORT2011 ACRover300	1.33500107	0.5881126	3.80 [1.20, 12.03]



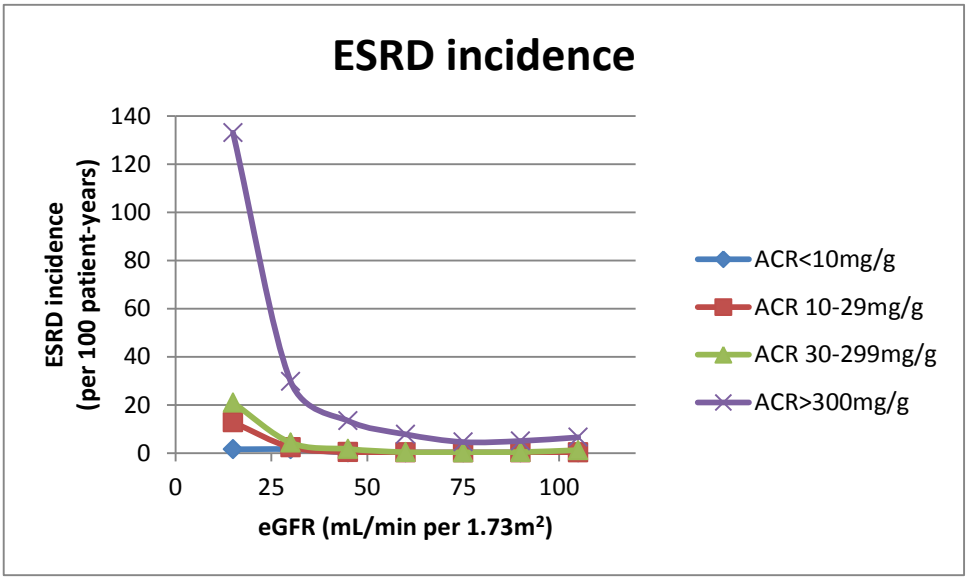
I.3.5 Incidence rates

Figure 68: Unadjusted incidence rates of progressive CKD per 1000 patient-years



Source: Gansevoort et al.[218] - High risk cohorts

Figure 69: Unadjusted incidence rates of end stage renal disease per 1000 patient-years



Source: Gansevoort et al.[218] - High risk cohorts

Figure 70: Unadjusted incidence rates of all-cause mortality per 1000 patient-years

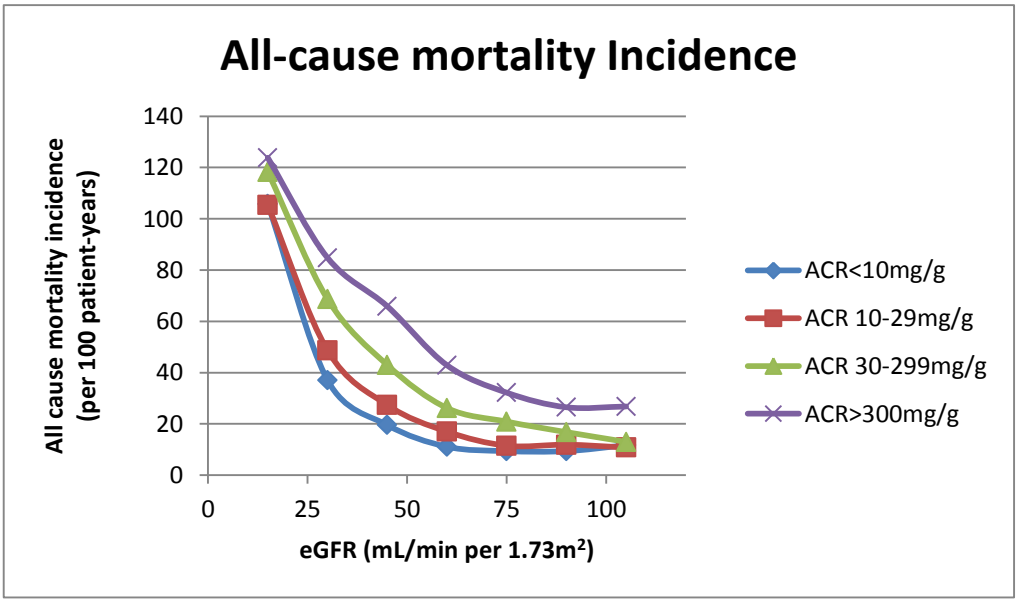
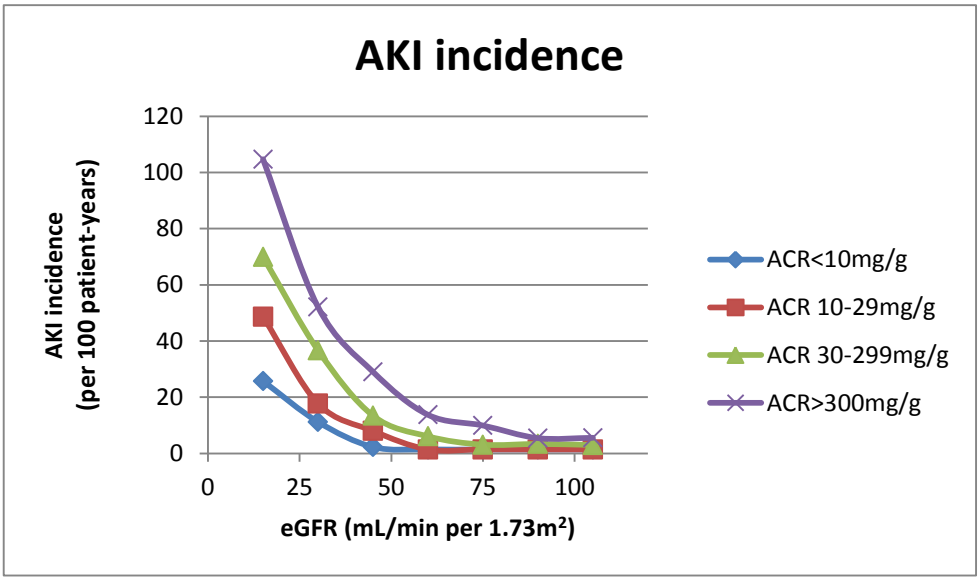


Figure 71: Unadjusted incidence rates of acute kidney injury per 1000 patient-years



Source: Gansevoort et al.[218] *- High risk cohorts*

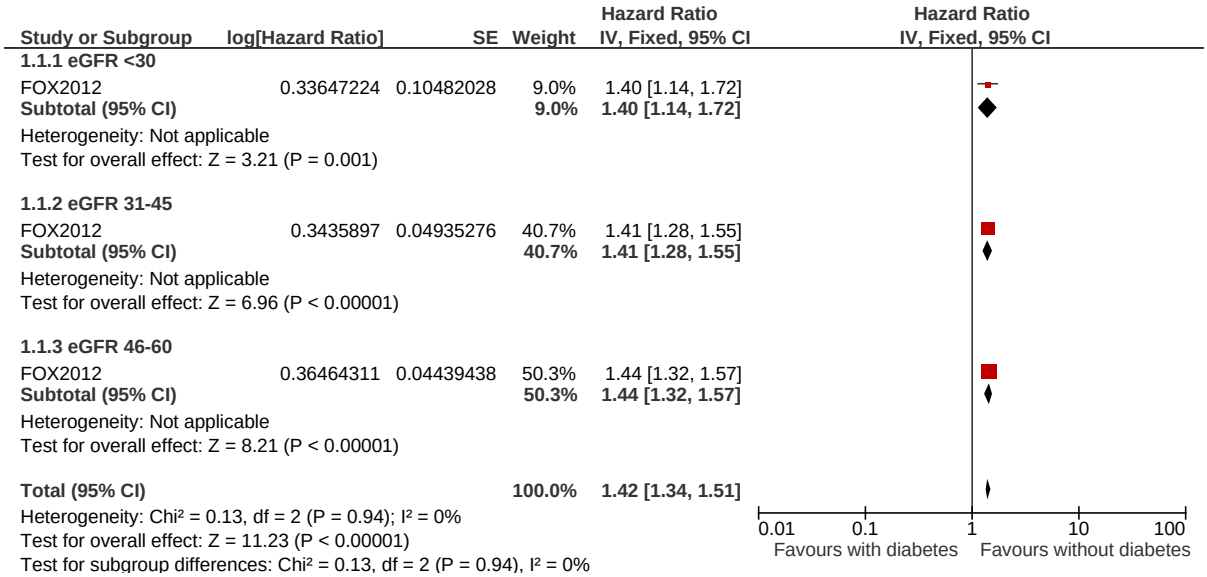
I.4 Cause of CKD – risk of adverse outcomes

NB. 'Favours' indicates lower risk in that group.

I.4.1 Diabetes

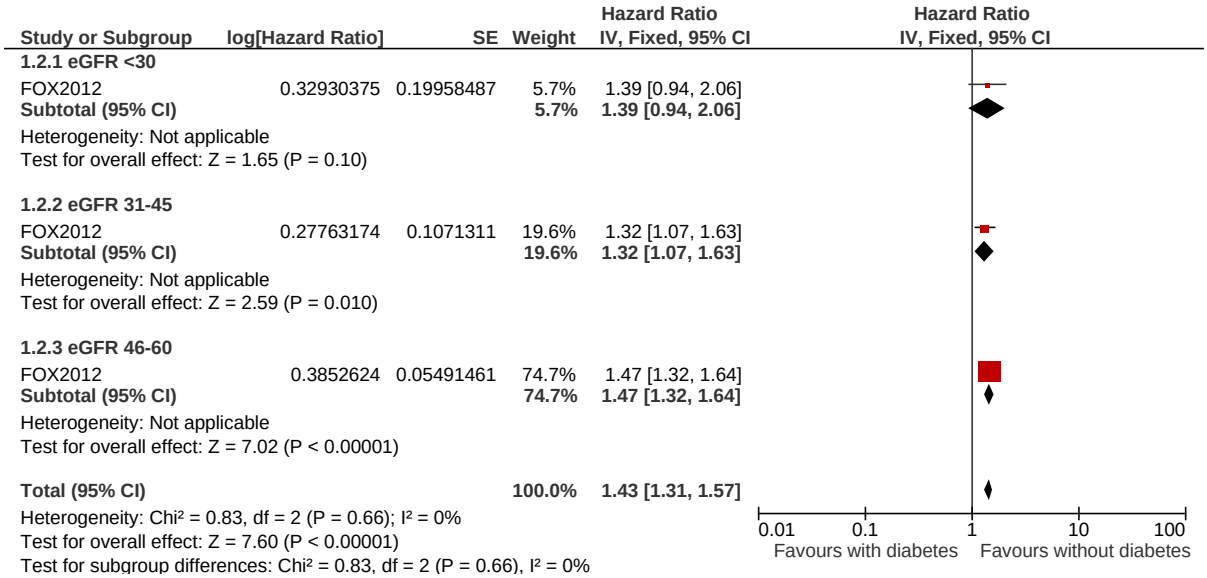
I.4.1.1 All-cause mortality

Figure 72: Risk of all-cause mortality in those with compared to those without diabetes, stratified by eGFR



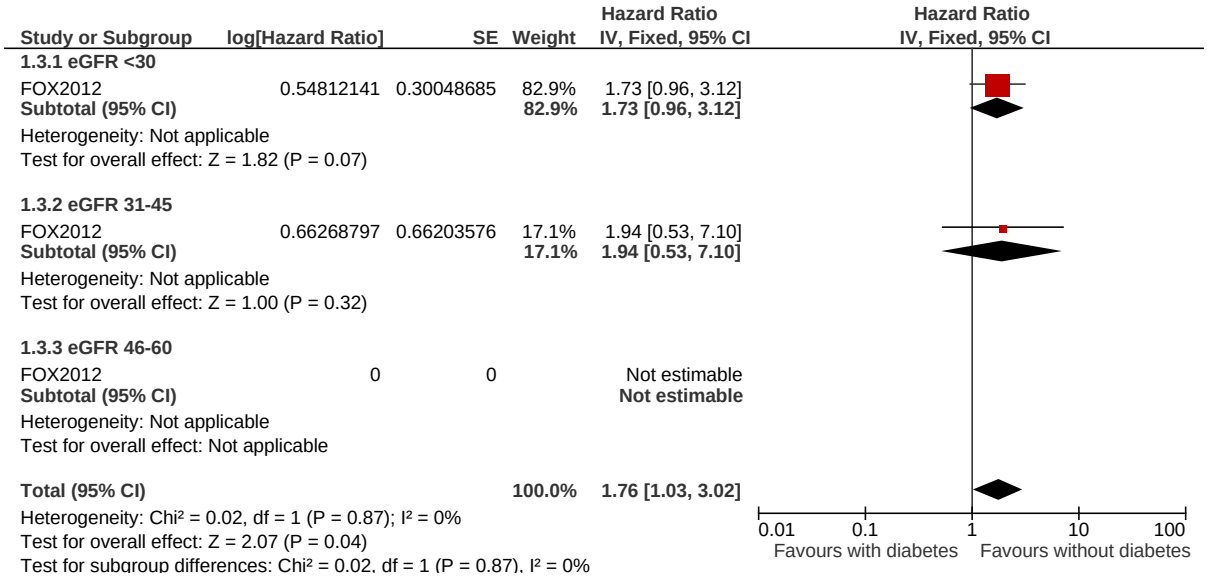
I.4.1.2 Cardiovascular mortality

Figure 73: Risk of cardiovascular mortality in those with compared to those without diabetes, stratified by eGFR



I.4.1.3 Progression of CKD (ESRD)

Figure 74: Risk of end stage renal disease in those with compared to those without diabetes, stratified by eGFR



I.4.2 Hypertension

I.4.2.1 All-cause mortality

Figure 75: Risk of all-cause mortality in those with compared to those without hypertension, stratified by eGFR

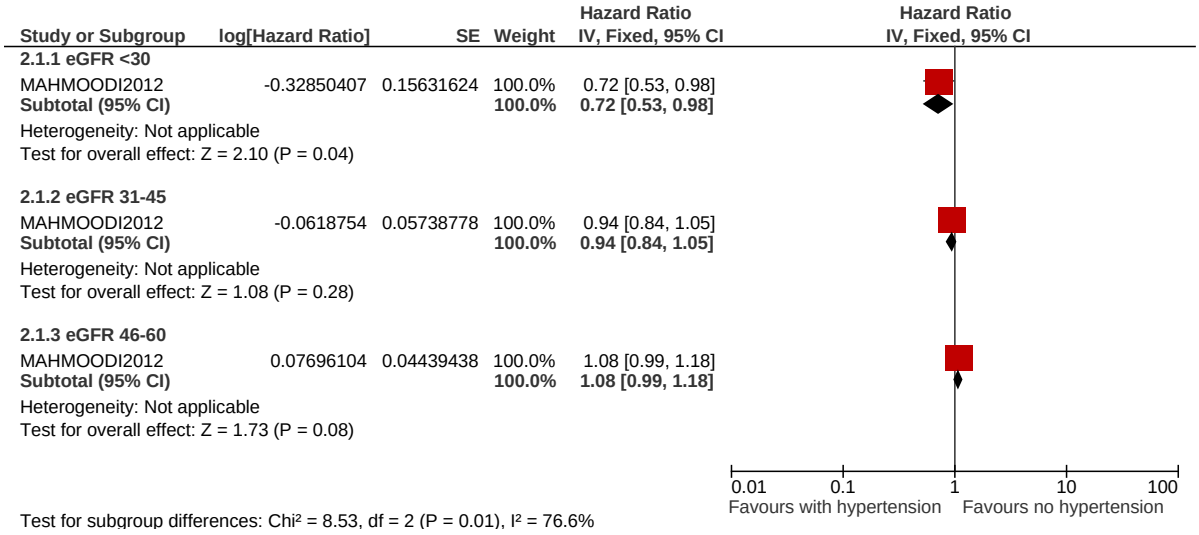
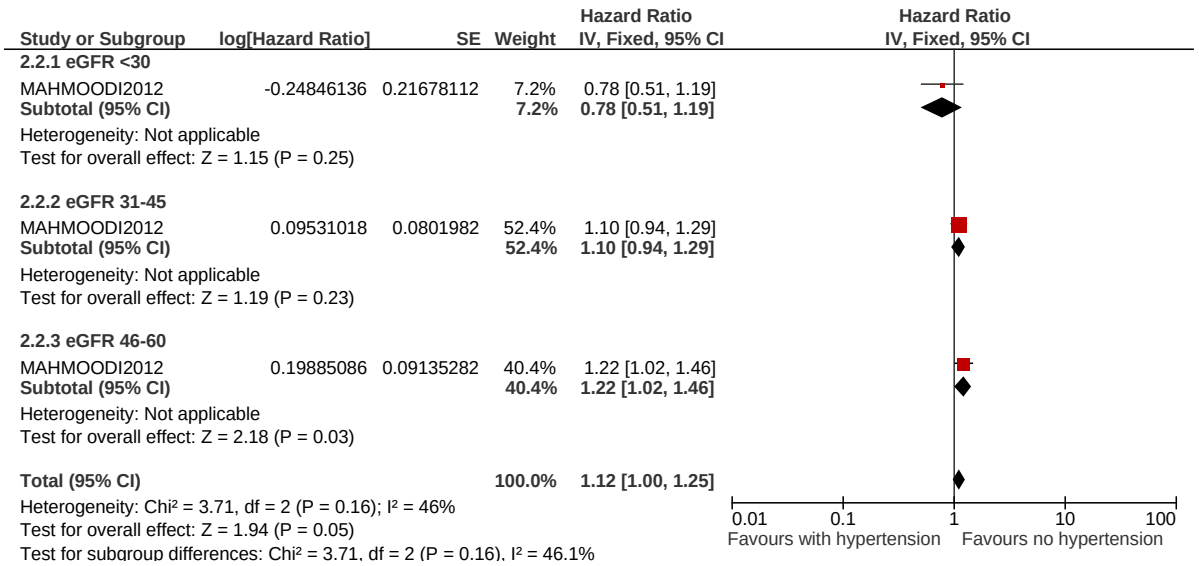
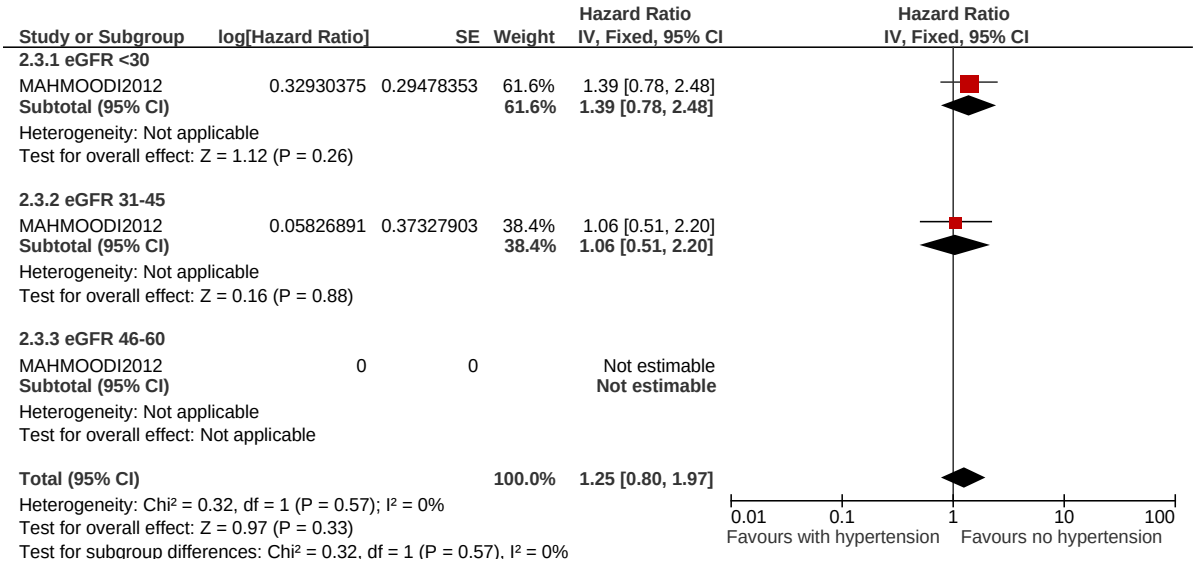


Figure 76: Risk of cardiovascular mortality in those with compared to those without hypertension, stratified by eGFR



I.4.2.2 Progression of CKD (ESRD)

Figure 77: Risk of ESRD in those with compared to those without hypertension, stratified by eGFR

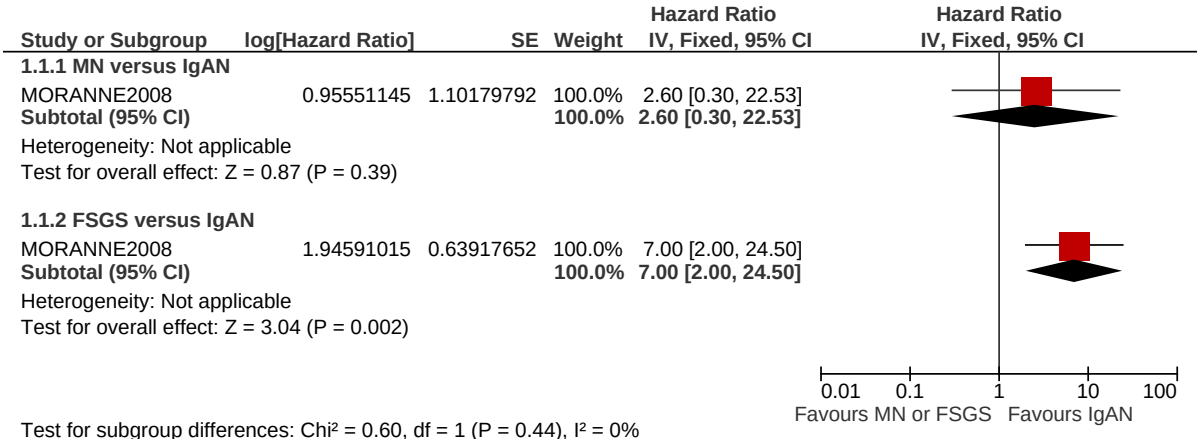


I.4.3 Glomerular disease

I.4.3.1 Progression of CKD (ESRD or dialysis)

Reference group: IgA nephropathy

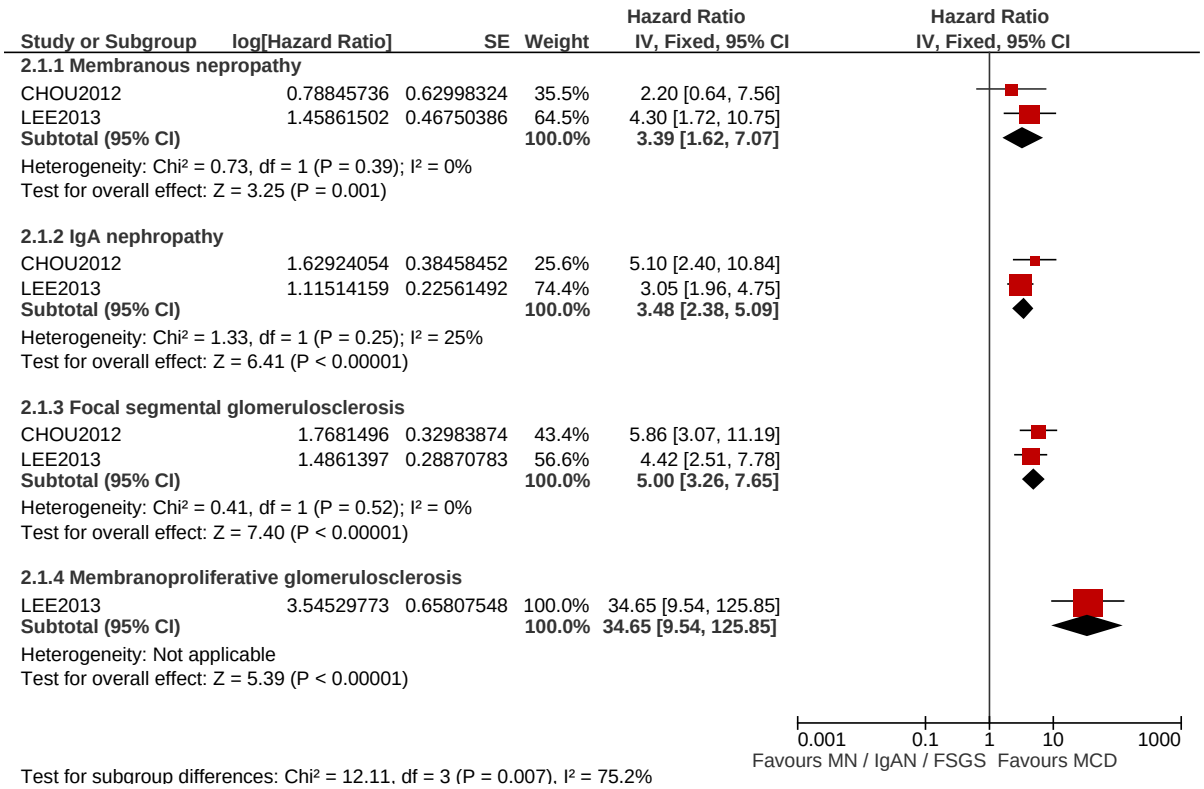
Figure 78: Risk of end stage renal disease stratified by type of glomerular disease on compared to IgAN



MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis

Reference group: minimal change disease

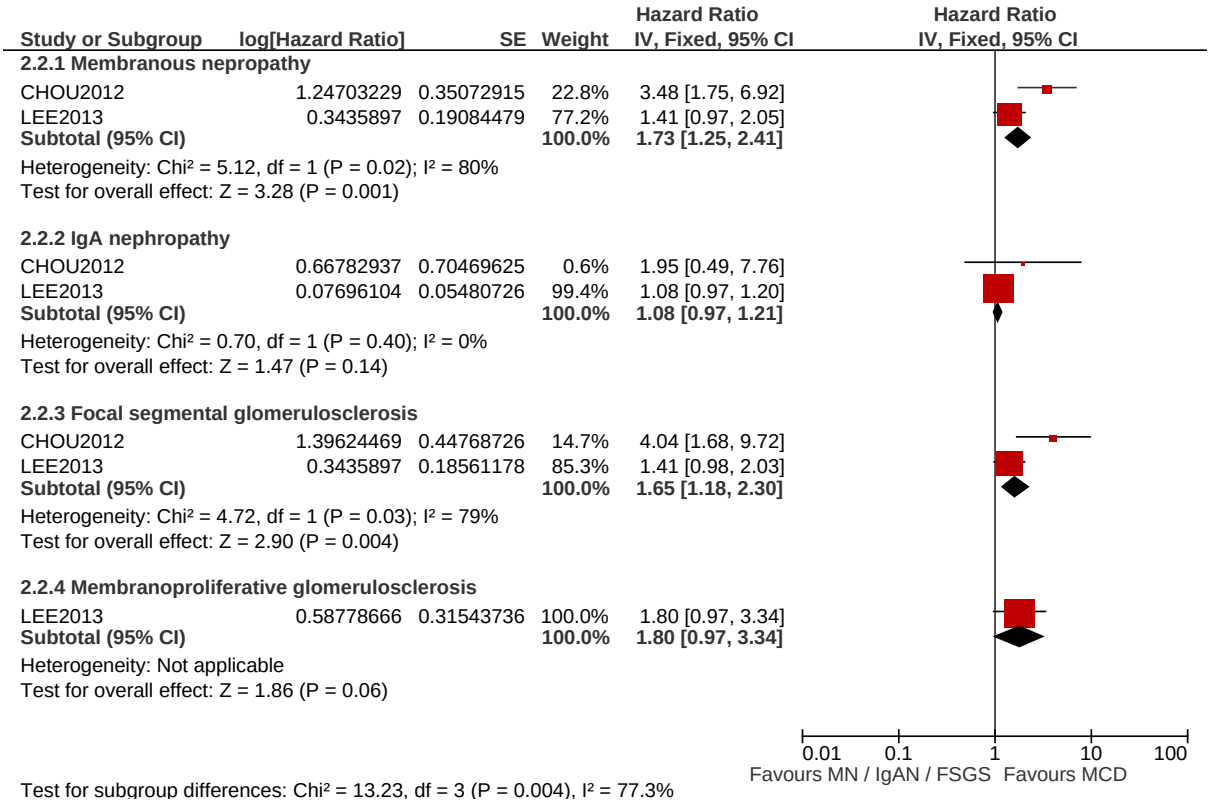
Figure 79: Risk of dialysis stratified by type of glomerular disease compared to minimal change disease



MCD = minimal change disease, MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis

Reference group: minimal change disease

Figure 80: Risk of mortality stratified by type of glomerular disease compared to minimal change disease



MCD = minimal change disease, MN = membranous nephropathy, IgAN = IgA nephropathy, FSGS = focal segmental glomerulosclerosis

I.4.4 Acute kidney injury

I.4.4.1 Acute tubular necrosis, acute renal failure or CKD versus control

Figure 81: Risk of progression to CKD stage 4

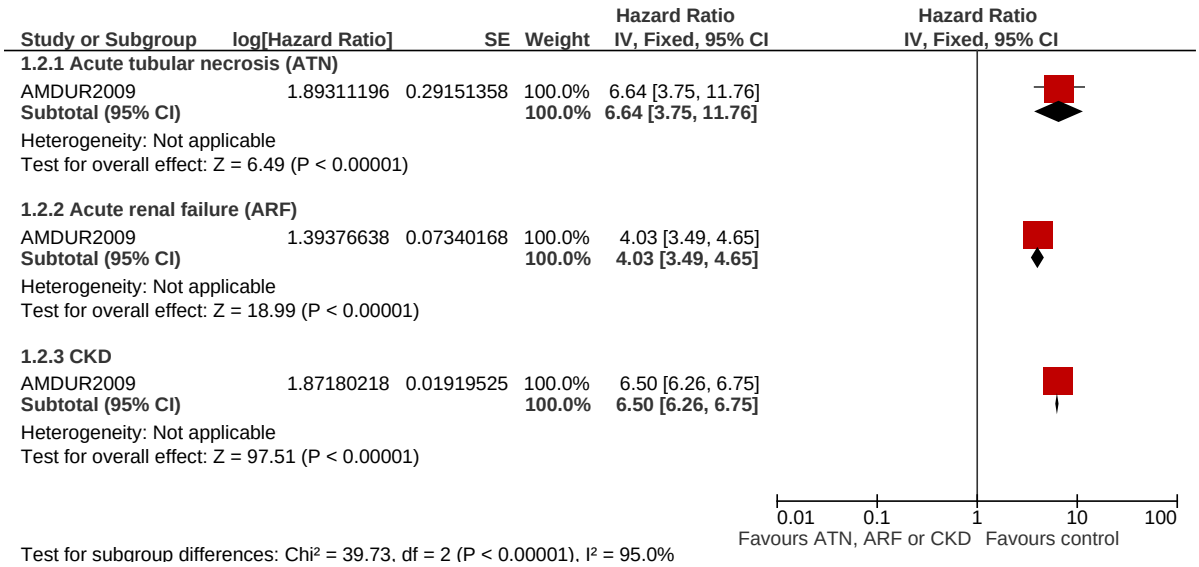
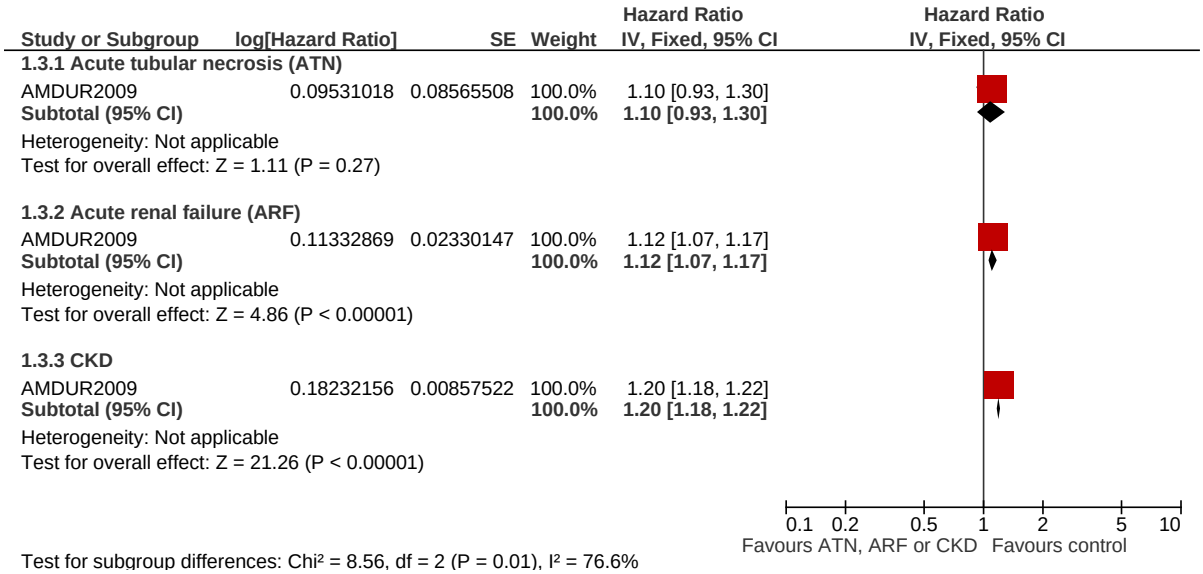


Figure 82: Risk of all-cause mortality

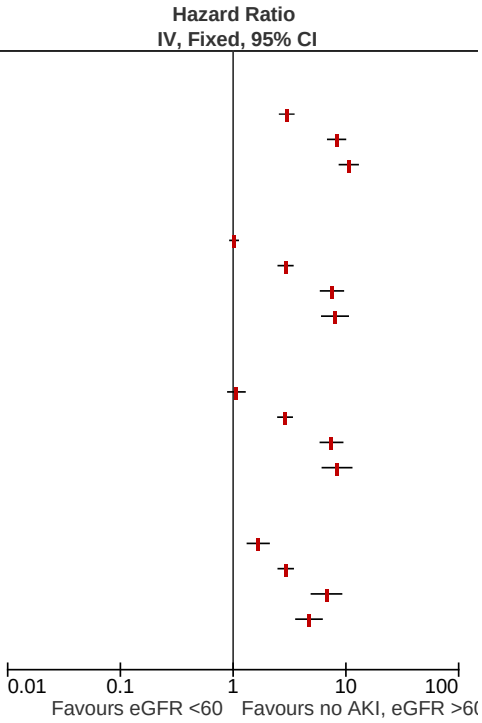


I.4.4.2 Stages of AKI stratified by eGFR level

Risk of In-hospital mortality

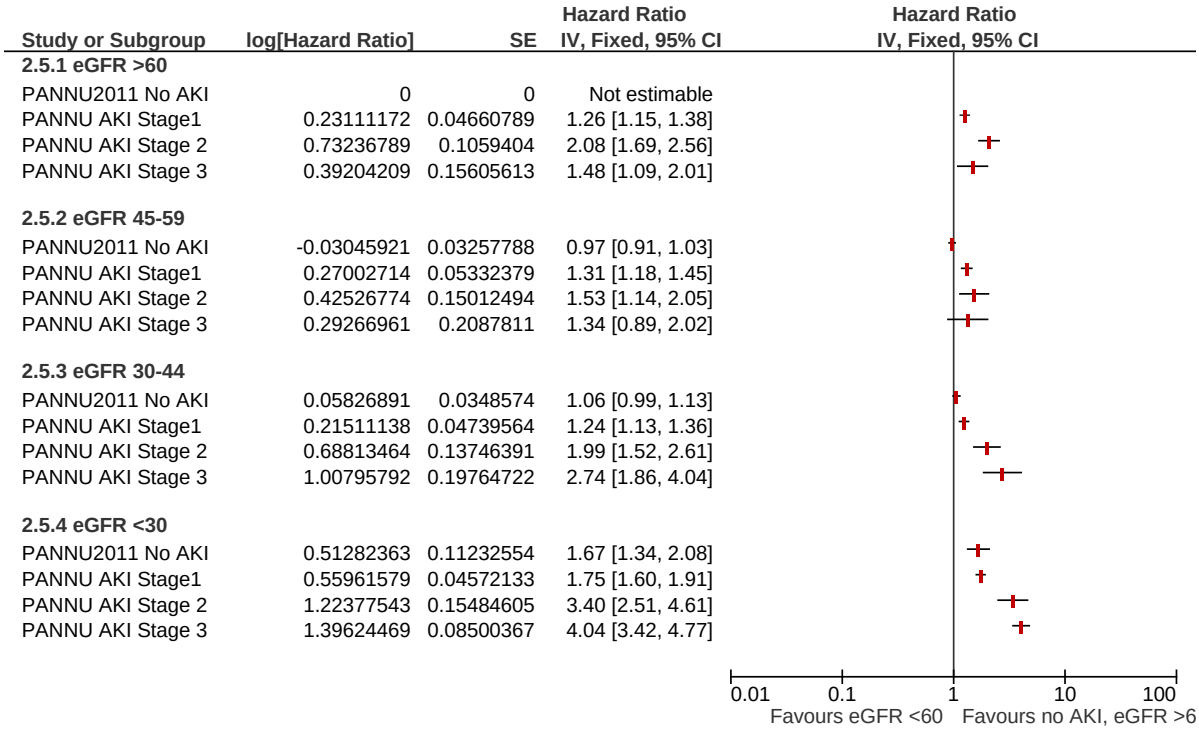
Figure 83: People without AKI or AKI stage 1-3, stratified by eGFR, compared to those with no AKI eGFR >60 ml/min/1.73 m^2

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
2.1.1 eGFR >60			
PANNU2011 No AKI	0	0	Not estimable
PANNU AKI Stage1	1.09527339	0.07327457	2.99 [2.59, 3.45]
PANNU AKI Stage 2	2.11384297	0.09154617	8.28 [6.92, 9.91]
PANNU AKI Stage 3	2.36273902	0.09707454	10.62 [8.78, 12.85]
2.1.2 eGFR 45-59			
PANNU2011 No AKI	0.01980263	0.04167323	1.02 [0.94, 1.11]
PANNU AKI Stage1	1.07158362	0.07516705	2.92 [2.52, 3.38]
PANNU AKI Stage 2	2.01889504	0.11759118	7.53 [5.98, 9.48]
PANNU AKI Stage 3	2.08069076	0.13731307	8.01 [6.12, 10.48]
2.1.3 eGFR 30-44			
PANNU2011 No AKI	0.06765865	0.08827671	1.07 [0.90, 1.27]
PANNU AKI Stage1	1.0612565	0.07396349	2.89 [2.50, 3.34]
PANNU AKI Stage 2	2.00955541	0.11539202	7.46 [5.95, 9.35]
PANNU AKI Stage 3	2.12226154	0.15189679	8.35 [6.20, 11.25]
2.1.4 eGFR <30			
PANNU2011 No AKI	0.51282363	0.11232554	1.67 [1.34, 2.08]
PANNU AKI Stage1	1.07500242	0.07691137	2.93 [2.52, 3.41]
PANNU AKI Stage 2	1.90805992	0.15645909	6.74 [4.96, 9.16]
PANNU AKI Stage 3	1.54968791	0.13570664	4.71 [3.61, 6.15]



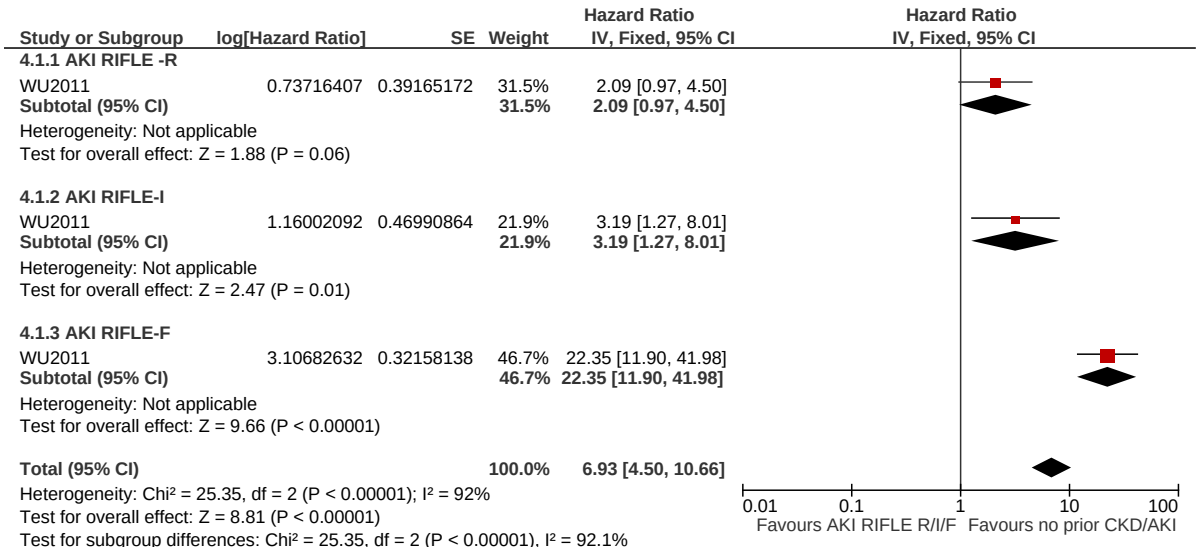
Risk of ESRD or all-cause mortality (after hospital discharge)

Figure 84: People without AKI, or AKI stage 1-3, stratified by eGFR, compared to those with no AKI eGFR >60 ml/min/1.73 m^2



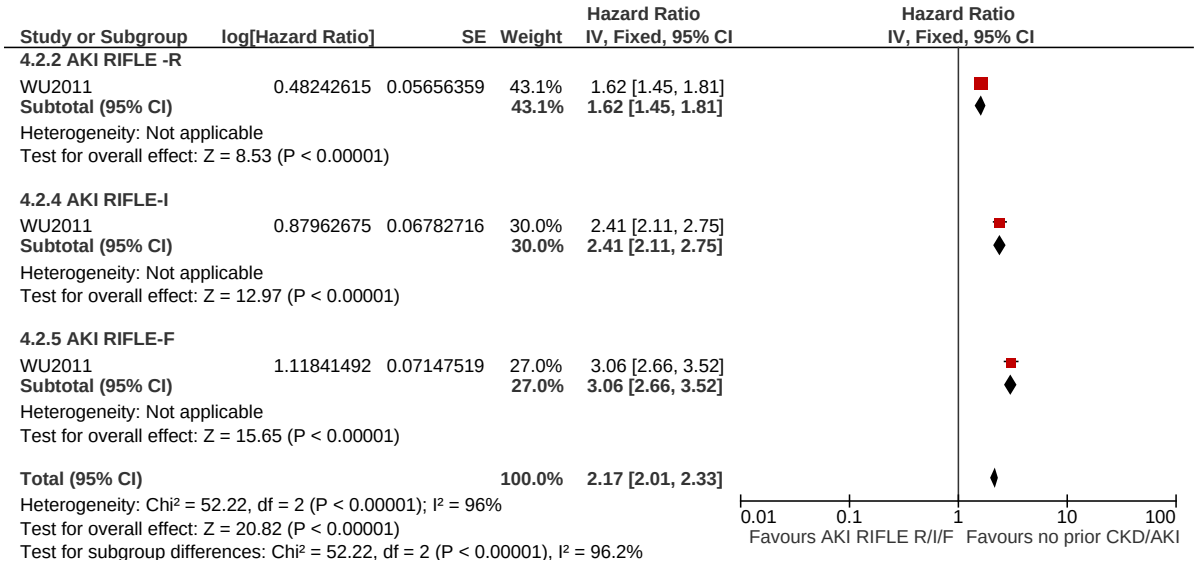
I.4.4.3 No prior CKD

Figure 85: Risk of dialysis in people without CKD stratified by stages of AKI compared to no AKI



AKI RIFLE grading: R= risk, I = injury, F = failure

Figure 86: Risk of mortality in people without CKD stratified by stages of AKI compared to no AKI



AKI RIFLE grading: R= risk, I = injury, F = failure

I.4.4.4 Prior CKD

Figure 87: Risk of long term dialysis in people with CKD stratified by presence of AKI compared to those without prior CKD or AKI

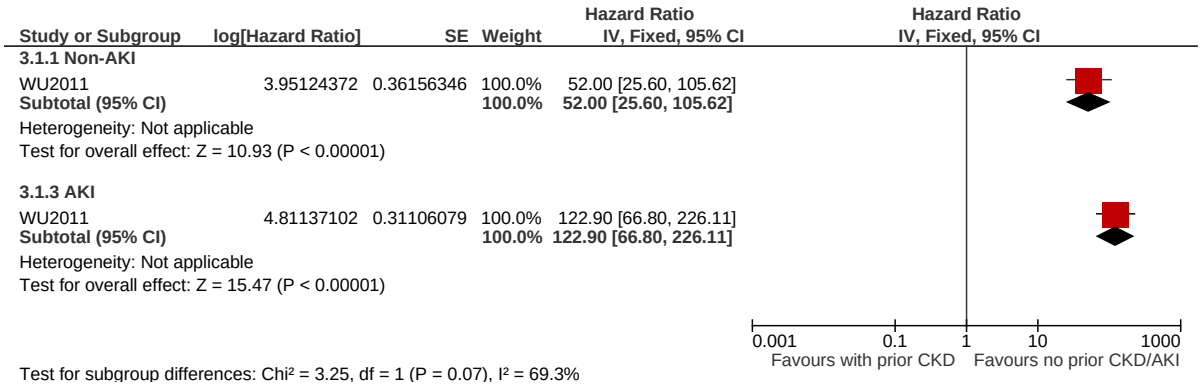
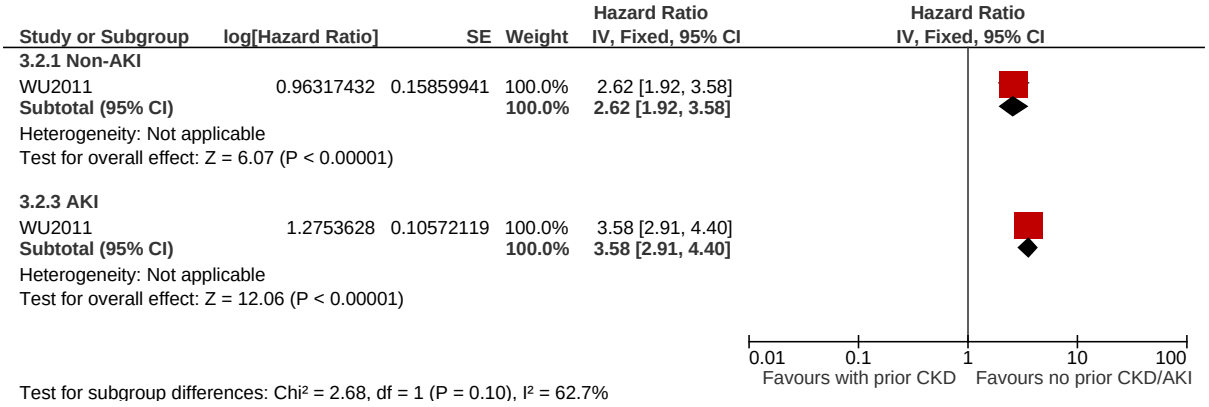


Figure 88: Risk of mortality in people with CKD stratified by presence of AKI compared to those without prior CKD or AKI



I.5 Frequency of Monitoring

I.5.1 Risk of progression

Figure 89: All-cause mortality (by one-year change in kidney function)

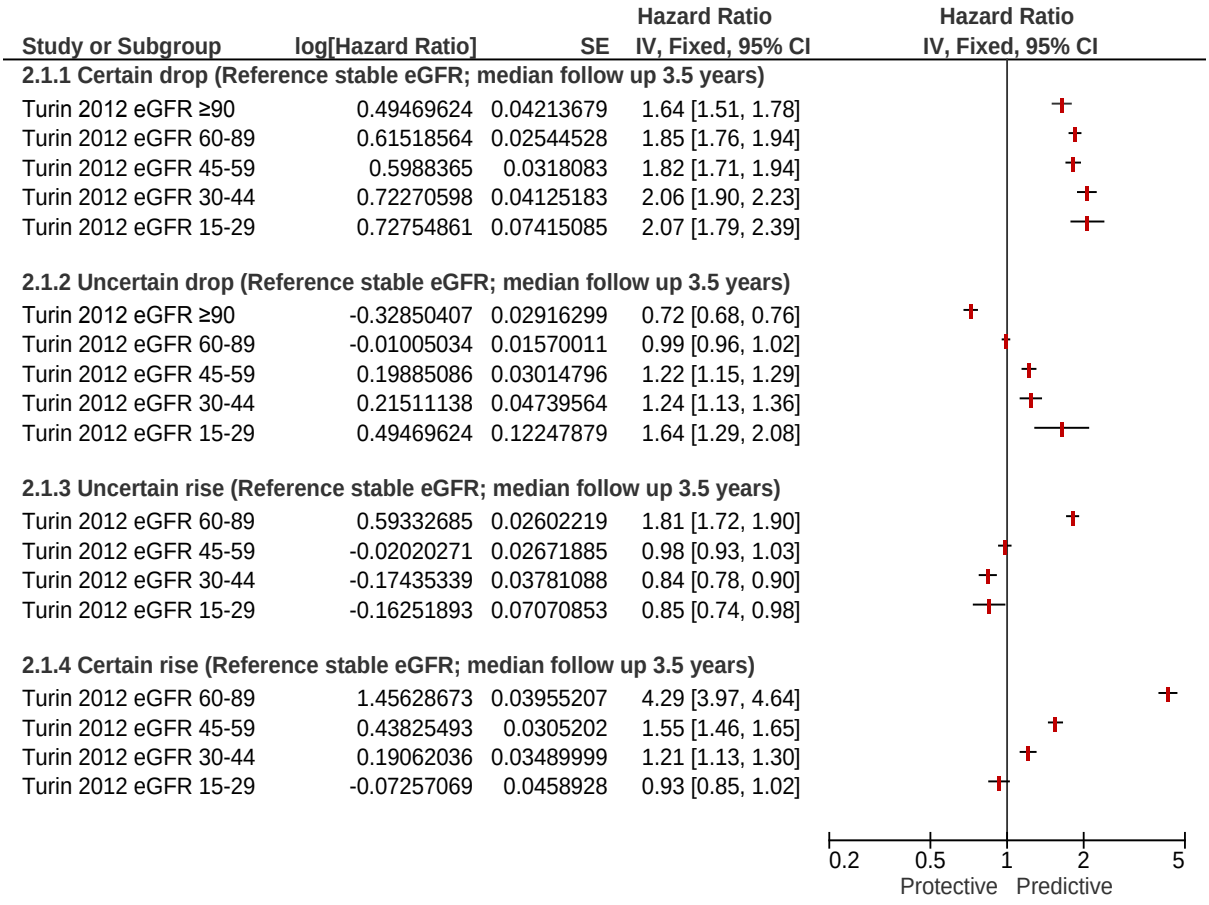


Figure 90: All-cause mortality

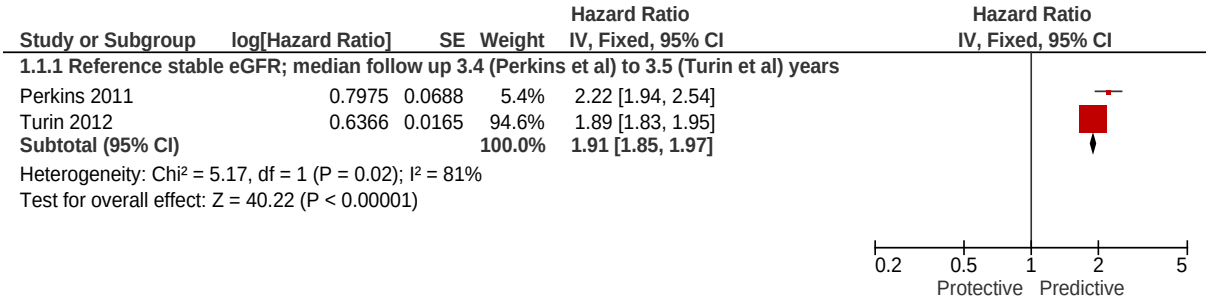


Figure 91: All-cause mortality (by eGFR subgroup) Reference group eGFR ≥105 ml/min/1.73 m^2

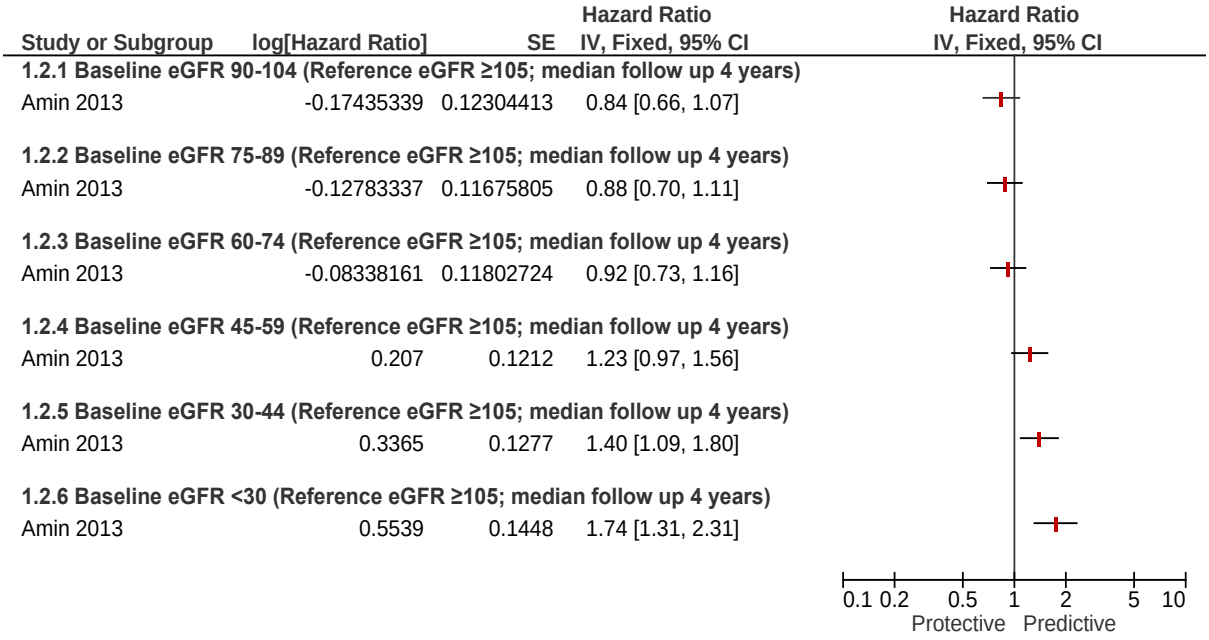


Figure 92: All-cause mortality (by eGFR subgroup) Reference group eGFR 45-59 ml/min/1.73 m^2

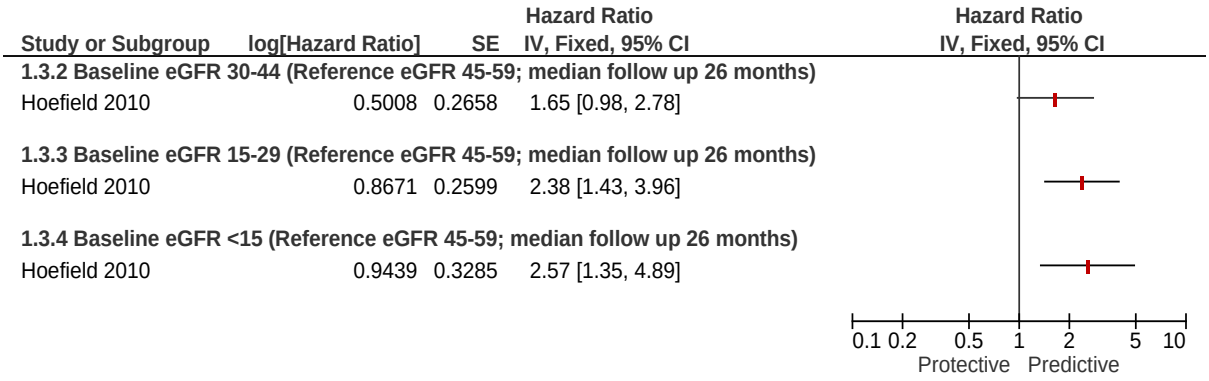


Figure 93: All-cause mortality by eGFR subgroup eGFR 25-29 ml/min/1.73 m^2

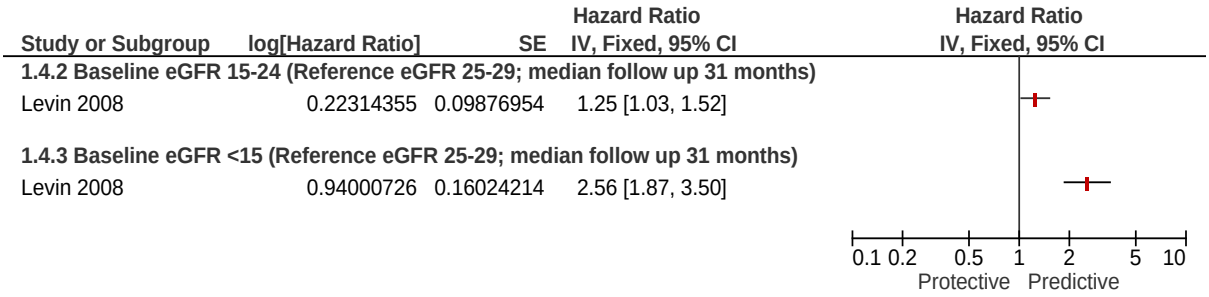


Figure 94: All-cause mortality (by level of proteinuria) Reference ACR <3

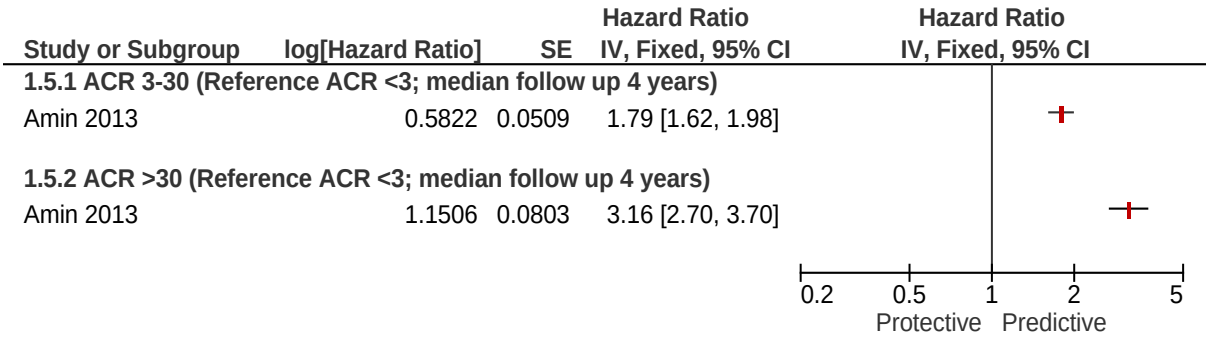


Figure 95: Progression of CKD – ESRD (by one- year change in kidney function) Reference = stable eGFR

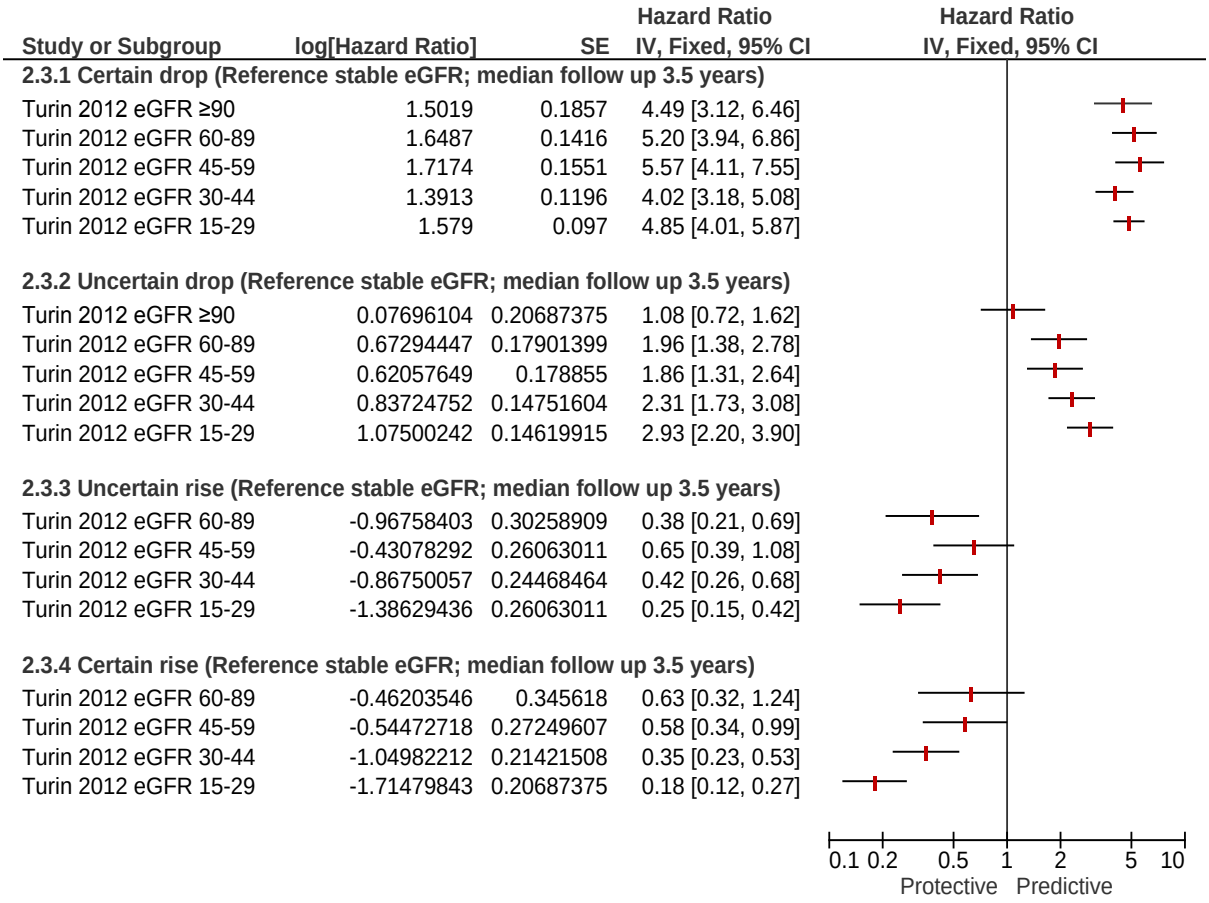


Figure 96: Progression of CKD (sustained drop of eGFR by 15 or to 10ml/min/1.73m²)(CKD Stage 3 and 4)

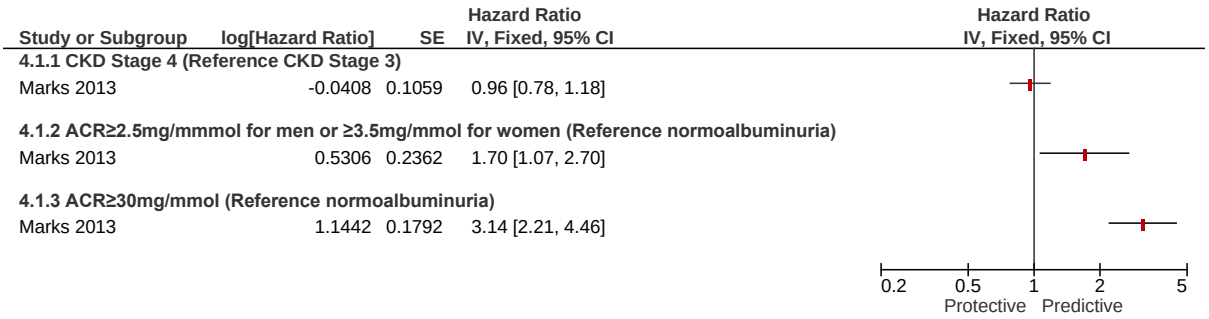


Figure 97: Progression (sustained 25% reduction in eGFR and CKD stage change)(CKD Stage 3 and 4)

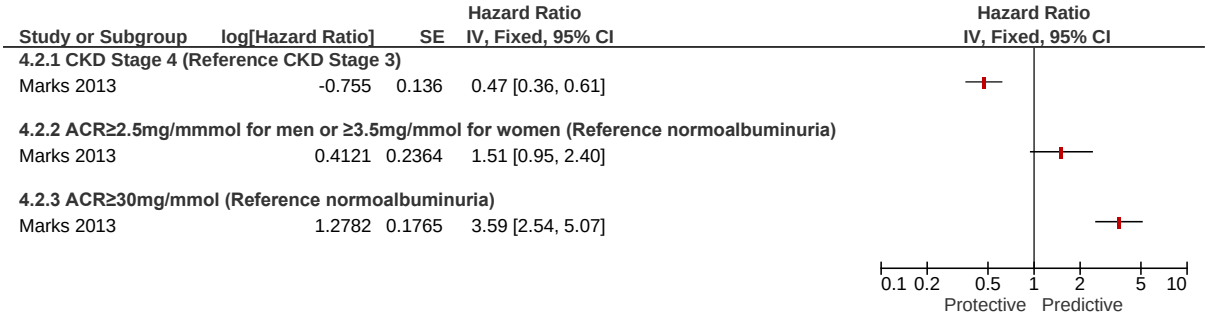


Figure 98: Progression of CKD – ESRD. Reference = stable eGFR

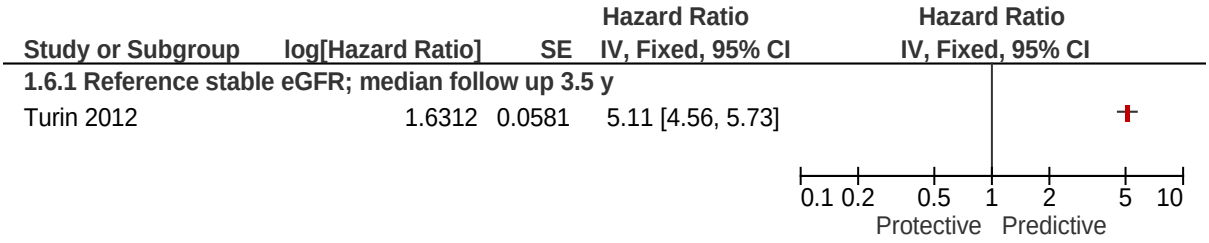


Figure 99: Progression of CKD – ESRD by eGFR subgroup. Reference eGFR ≥105 ml/min/1.73 m^2

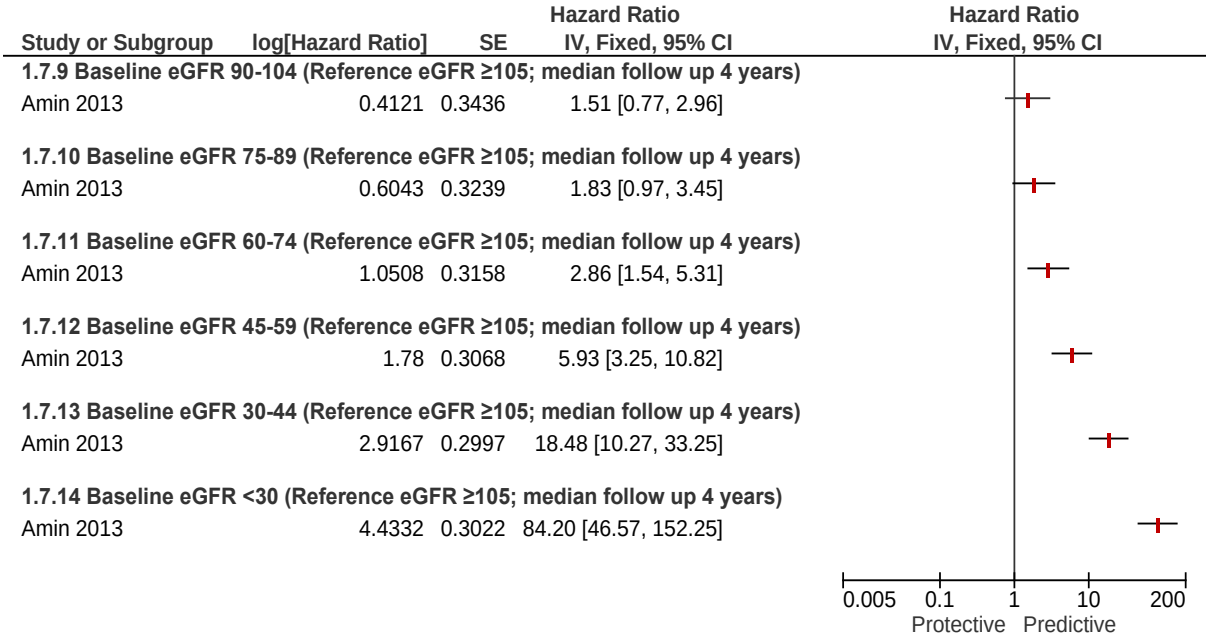


Figure 100: Progression of CKD – RRT (CKD Stage 3 and 4)

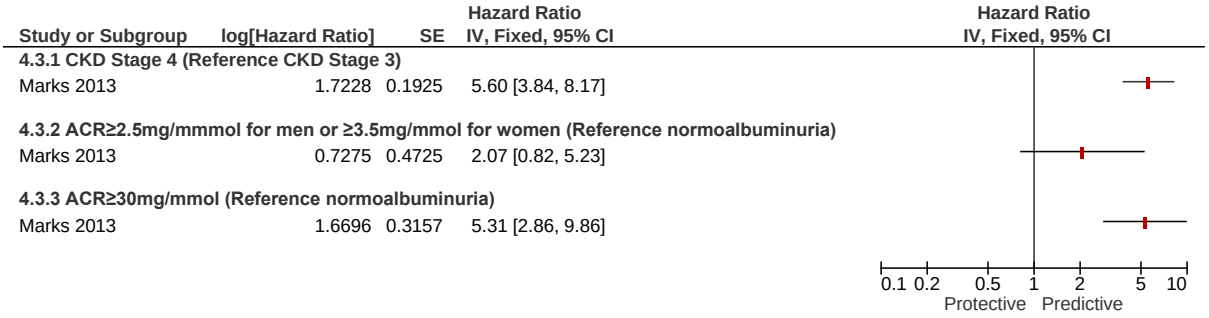


Figure 101: Progression of CKD – RRT (by eGFR subgroup) Reference eGFR 45-59 ml/min/1.73 m^2

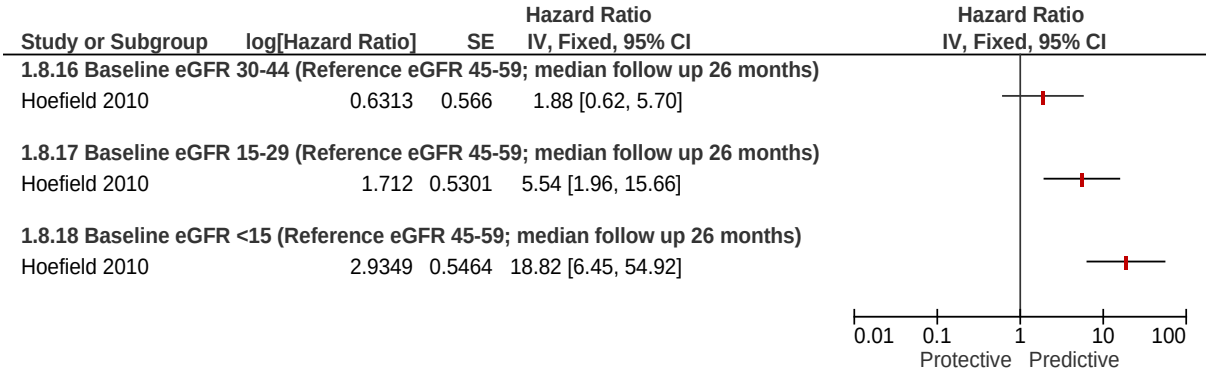


Figure 102: Progression of CKD – RRT (by eGFR subgroup) Reference eGFR 25-29 ml/min/1.73 m^2

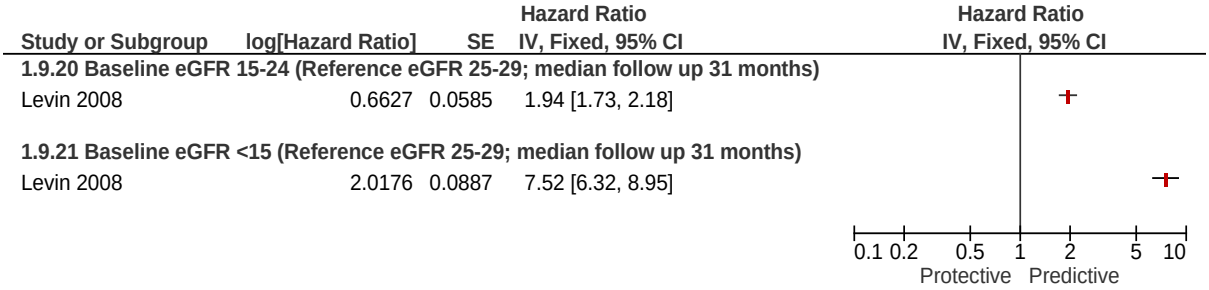


Figure 103: Progression of CKD - ESRD (by level of proteinuria) Reference ACR <3

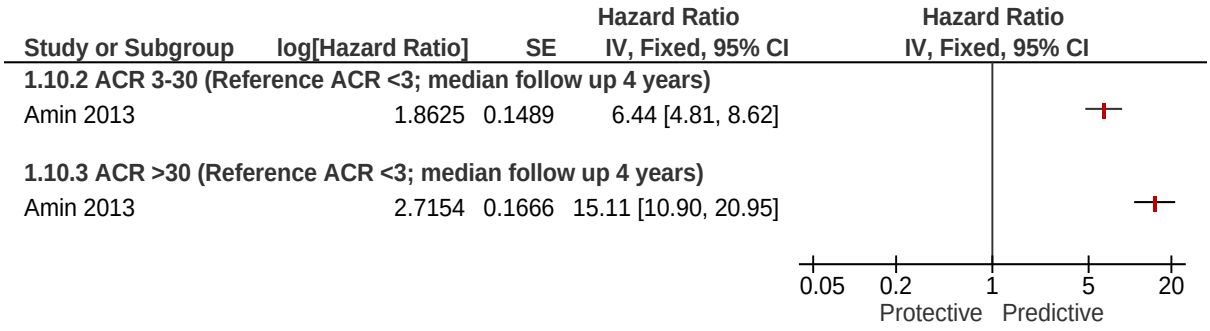
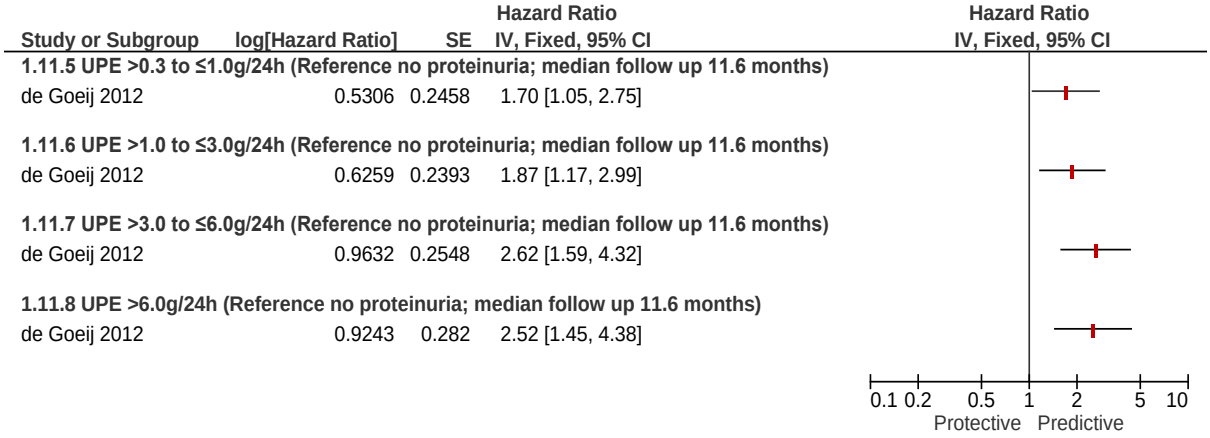
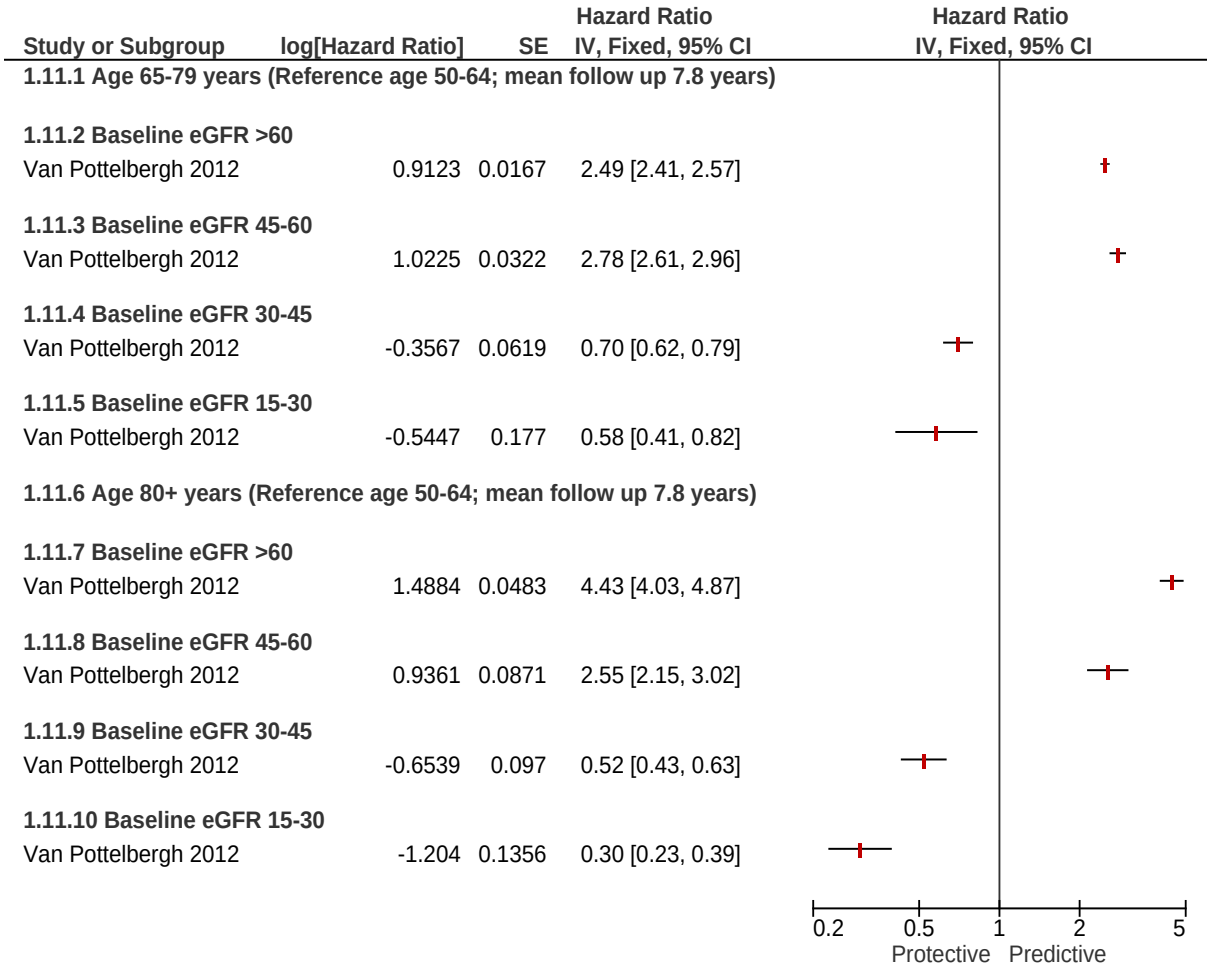


Figure 104: Progression of CKD - RRT (by level of proteinuria) Reference no proteinuria



UPE = urinary protein excretion; a UPE of 0.5g/24h is approximately equivalent to an ACR of 30mg/mmol and a UPE of 1.0g/24h is approximately equivalent to an ACR of 70mg/mmol.

Figure 105: Progression of CKD – ESRD by age and eGFR subgroups



I.5.2 Probability of progression

Figure 106: Probability of mortality at different time points by eGFR subgroup versus reference group (eGFR ≥105 ml/min/1.73 m^2)

Study or Subgroup	Lower probability Events	Total	Reference (eGFR ≥105) Events	Total	Risk Difference M-H, Fixed, 95% CI
3.7.1 6 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	0	5383	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 30-44	26	2555	0	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR ≤29	7	680	0	5714	0.01 [0.00, 0.02]
3.7.2 12 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	54	5383	0	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR 30-44	51	2555	0	5714	0.02 [0.01, 0.03]
Amin 2013 eGFR ≤29	20	680	0	5714	0.03 [0.02, 0.04]
3.7.3 18 months					
Amin 2013 eGFR 90-104	92	9158	57	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	104	10354	57	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	89	8917	57	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	108	5383	57	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR 30-44	77	2555	57	5714	0.02 [0.01, 0.03]
Amin 2013 eGFR ≤29	41	680	57	5714	0.05 [0.03, 0.07]
3.7.4 24 months					
Amin 2013 eGFR 90-104	92	9158	57	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	104	10354	57	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	178	8917	57	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR 45-59	161	5383	57	5714	0.02 [0.01, 0.03]
Amin 2013 eGFR 30-44	102	2555	57	5714	0.03 [0.02, 0.04]
Amin 2013 eGFR ≤29	54	680	57	5714	0.07 [0.05, 0.09]

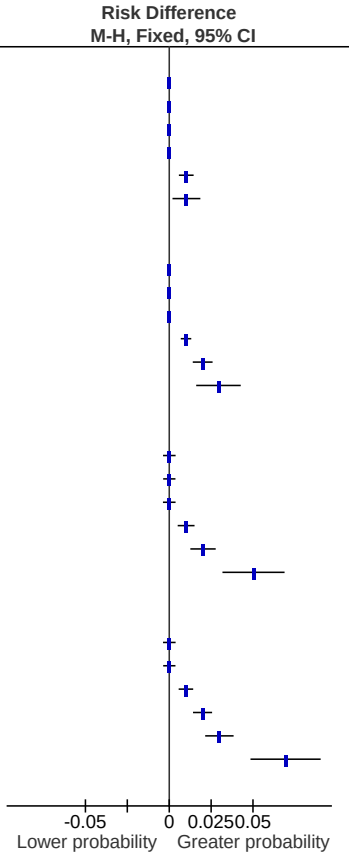


Figure 107: Probability of mortality at different time points by eGFR subgroup versus reference group (eGFR ≥44-59 ml/min/1.73 m^2)

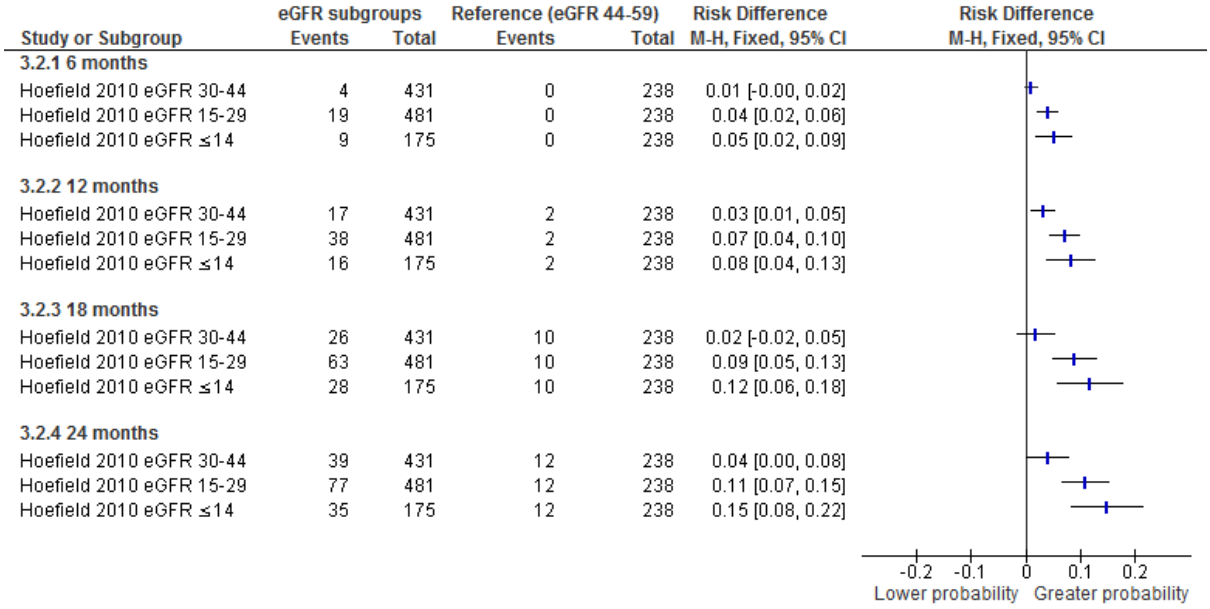


Figure 108: Probability of mortality at different time points by eGFR subgroup versus reference group (eGFR 25-29 ml/min/1.73 m^2)

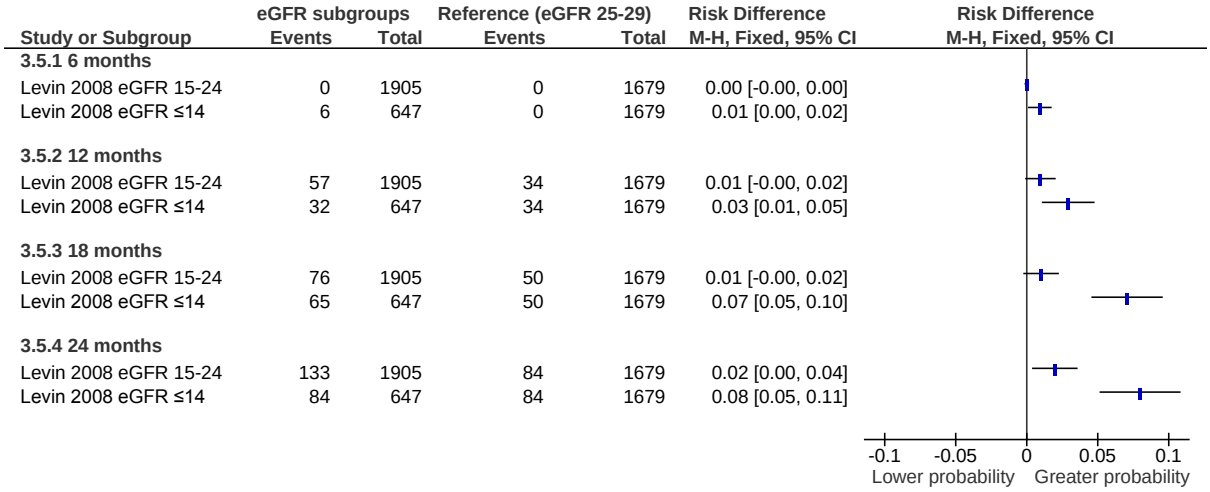


Figure 109: Probability of ESRD at different time points by eGFR subgroup versus reference group (eGFR ≥105 ml/min/1.73 m^2)

Study or Subgroup	Lower probability Events	Total	Reference (eGFR ≥ 105) Events	Total	Risk Difference M-H, Fixed, 95% CI
3.9.1 6 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	0	5383	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 30-44	0	2555	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR ≤29	34	680	0	5714	0.05 [0.03, 0.07]
3.9.2 12 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	0	5383	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 30-44	26	2555	0	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR ≤29	68	680	0	5714	0.10 [0.08, 0.12]
3.9.3 18 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	0	5383	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 30-44	26	2555	0	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR ≤29	102	680	0	5714	0.15 [0.12, 0.18]
3.9.4 24 months					
Amin 2013 eGFR 90-104	0	9158	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 75-89	0	10354	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 60-74	0	8917	0	5714	0.00 [-0.00, 0.00]
Amin 2013 eGFR 45-59	54	5383	0	5714	0.01 [0.01, 0.01]
Amin 2013 eGFR 30-44	51	2555	0	5714	0.02 [0.01, 0.03]
Amin 2013 eGFR ≤29	136	680	0	5714	0.20 [0.17, 0.23]

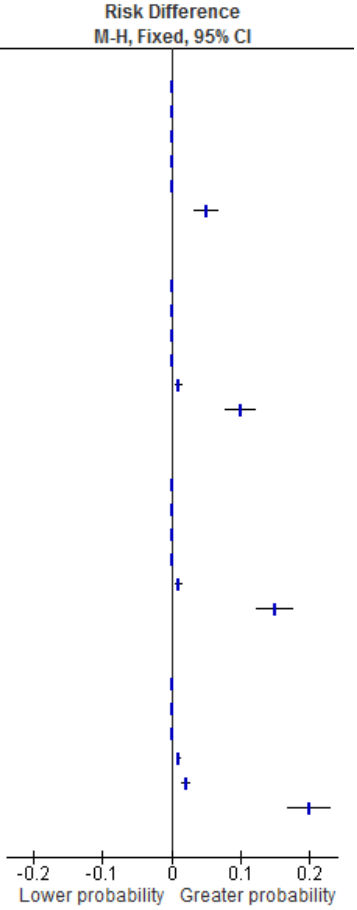


Figure 110: Probability of RRT at different time points by eGFR subgroup versus reference group (eGFR ≥44-59 ml/min/1.73 m^2)

Study or Subgroup	eGFR subgroups Events	Total	Reference (eGFR 44-59) Events	Total	Risk Difference M-H, Fixed, 95% CI
3.1.1 6 months					
Hoefield 2010 eGFR 30-44	0	431	0	238	0.00 [-0.01, 0.01]
Hoefield 2010 eGFR 15-29	5	481	0	238	0.01 [-0.00, 0.02]
Hoefield 2010 eGFR ≤14	19	175	0	238	0.11 [0.06, 0.16]
3.1.2 12 months					
Hoefield 2010 eGFR 30-44	0	431	0	238	0.00 [-0.01, 0.01]
Hoefield 2010 eGFR 15-29	14	481	0	238	0.03 [0.01, 0.05]
Hoefield 2010 eGFR ≤14	53	175	0	238	0.30 [0.23, 0.37]
3.1.3 18 months					
Hoefield 2010 eGFR 30-44	4	431	2	238	0.00 [-0.01, 0.02]
Hoefield 2010 eGFR 15-29	19	481	2	238	0.03 [0.01, 0.05]
Hoefield 2010 eGFR ≤14	75	175	2	238	0.42 [0.35, 0.49]
3.1.4 24 months					
Hoefield 2010 eGFR 30-44	9	431	5	238	-0.00 [-0.02, 0.02]
Hoefield 2010 eGFR 15-29	29	481	5	238	0.04 [0.01, 0.07]
Hoefield 2010 eGFR ≤14	81	175	5	238	0.44 [0.37, 0.52]

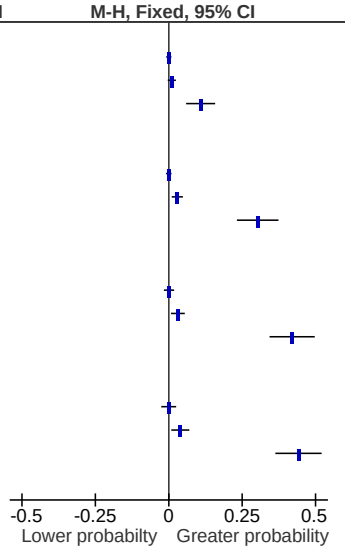


Figure 111: Probability of RRT at different time points by eGFR subgroup versus reference group (eGFR 25-29 ml/min/1.73 m^2)

Study or Subgroup	eGFR subgroups Events	Total	Reference (eGFR 25-29) Events	Total	Risk Difference M-H, Fixed, 95% CI
3.4.1 6 months					
Levin 2008 eGFR 15-24	19	1905	0	1679	0.01 [0.01, 0.01]
Levin 2008 eGFR ≤14	65	647	0	1679	0.10 [0.08, 0.12]
3.4.2 12 months					
Levin 2008 eGFR 15-24	191	1905	50	1679	0.07 [0.05, 0.09]
Levin 2008 eGFR ≤14	207	647	50	1679	0.29 [0.25, 0.33]
3.4.3 18 months					
Levin 2008 eGFR 15-24	381	1905	101	1679	0.14 [0.12, 0.16]
Levin 2008 eGFR ≤14	311	647	101	1679	0.42 [0.38, 0.46]
3.4.4 24 months					
Levin 2008 eGFR 15-24	476	1905	168	1679	0.15 [0.13, 0.17]
Levin 2008 eGFR ≤14	362	647	168	1679	0.46 [0.42, 0.50]

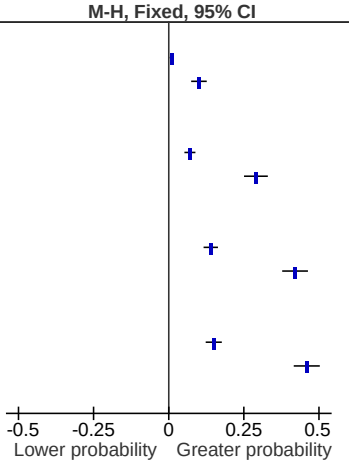


Figure 112: Probability of mortality at different time points by ACR subgroup versus reference group (ACR <3mg/mmol)

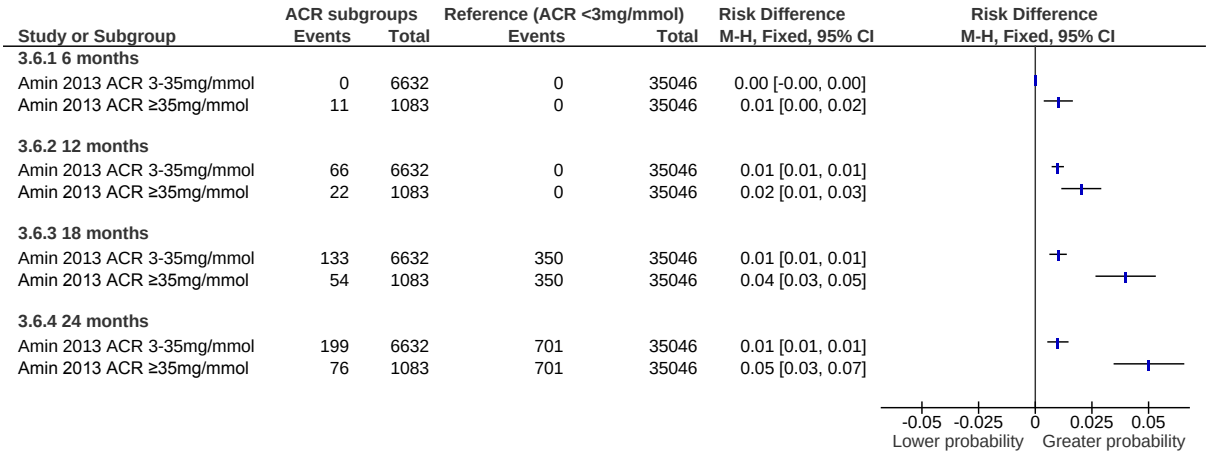


Figure 113: Probability of ESRD at different time points by ACR subgroup versus reference group (ACR <3mg/mmol)

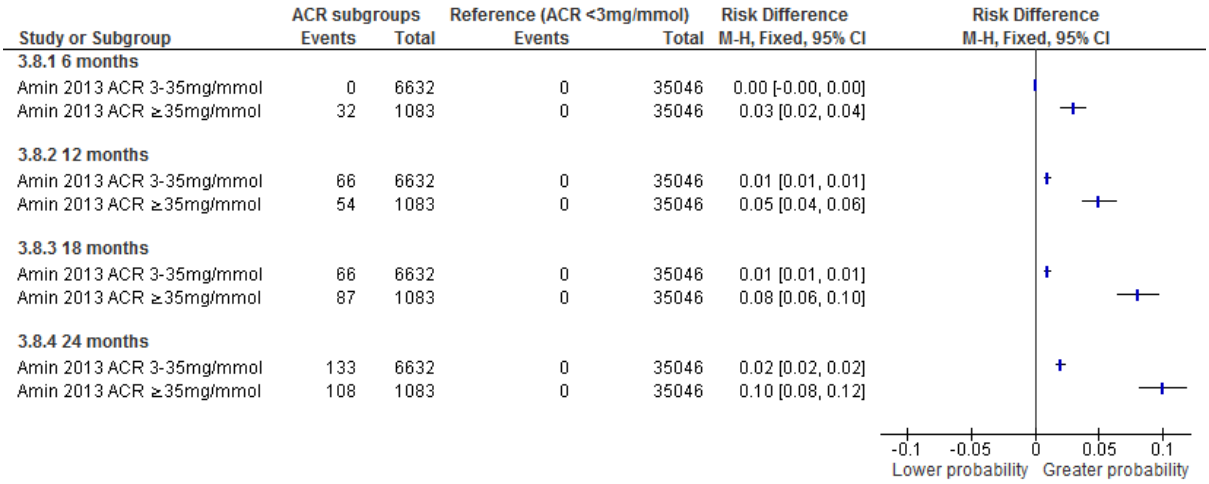
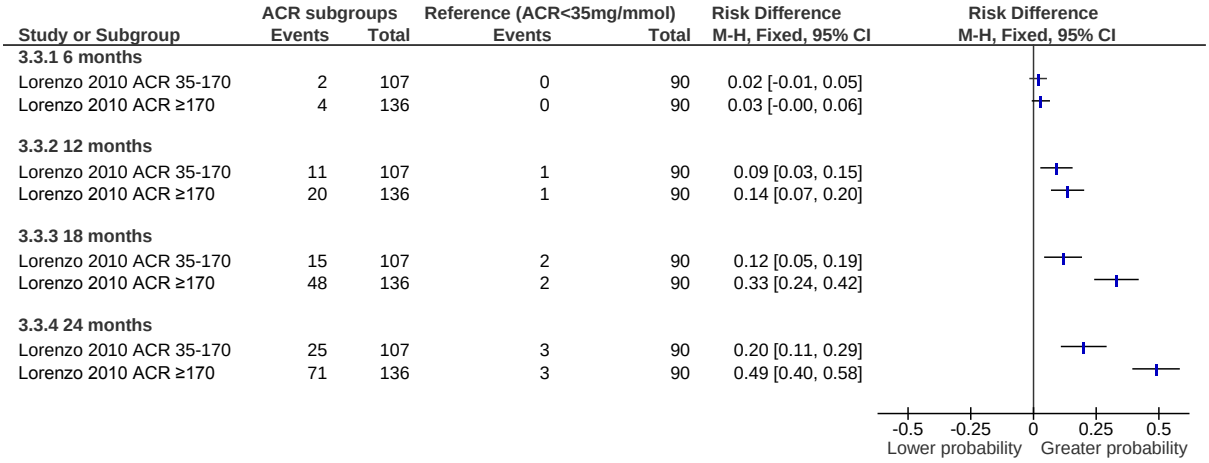


Figure 114: Probability of RRT at different time points by ACR subgroup versus reference group (ACR <35mg/mmol)



I.6 Progression of CKD after acute kidney injury

I.6.1 Risk of ESRD or CKD progression with an episode of AKI

Figure 115: Risk of progression to CKD stage 3

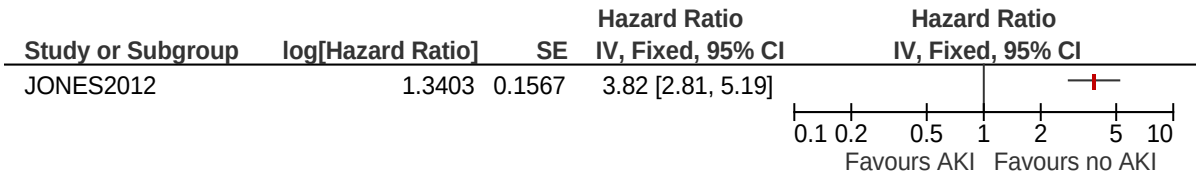


Figure 116: Risk of progression to CKD stage 4 (control group = people with acute admission for MI or pneumonia with no ARF or ATN)

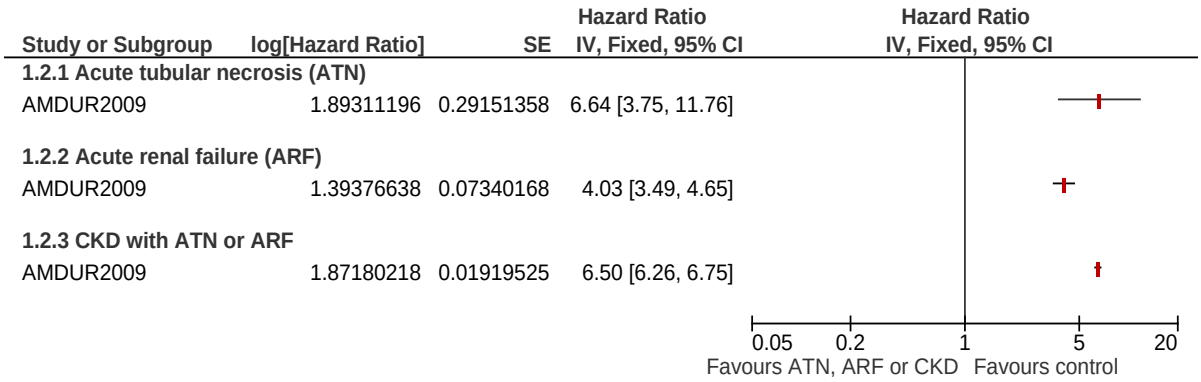


Figure 117: Risk of progression to CKD stage 4 in people with diabetes

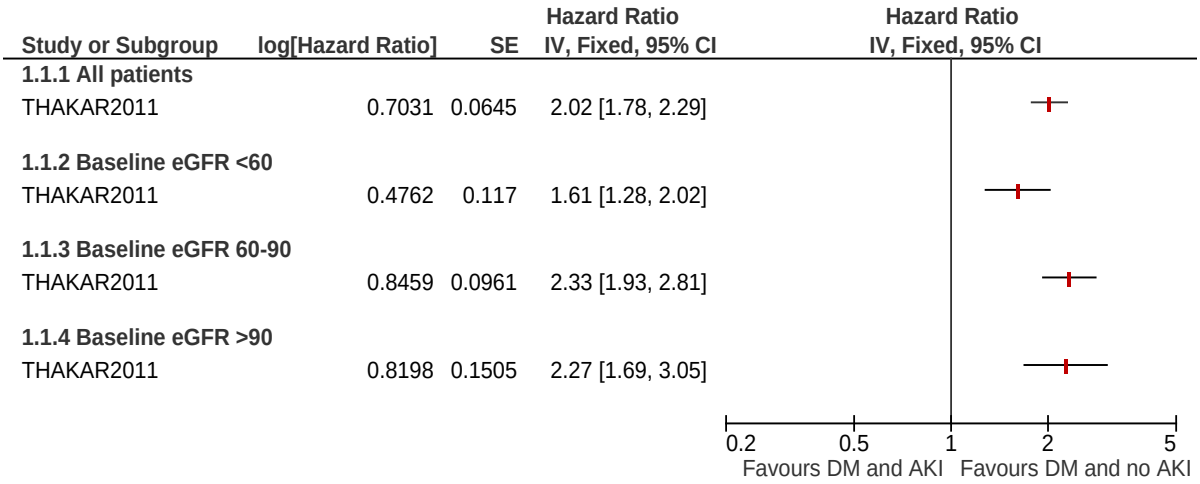
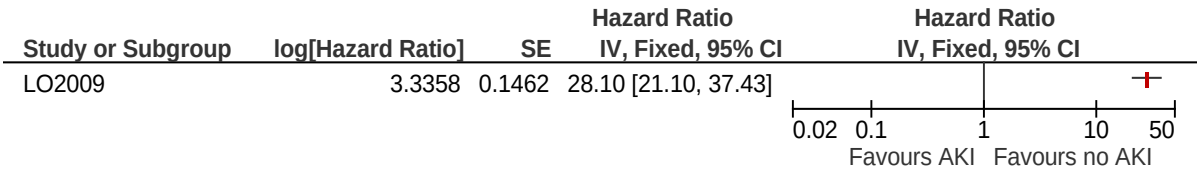
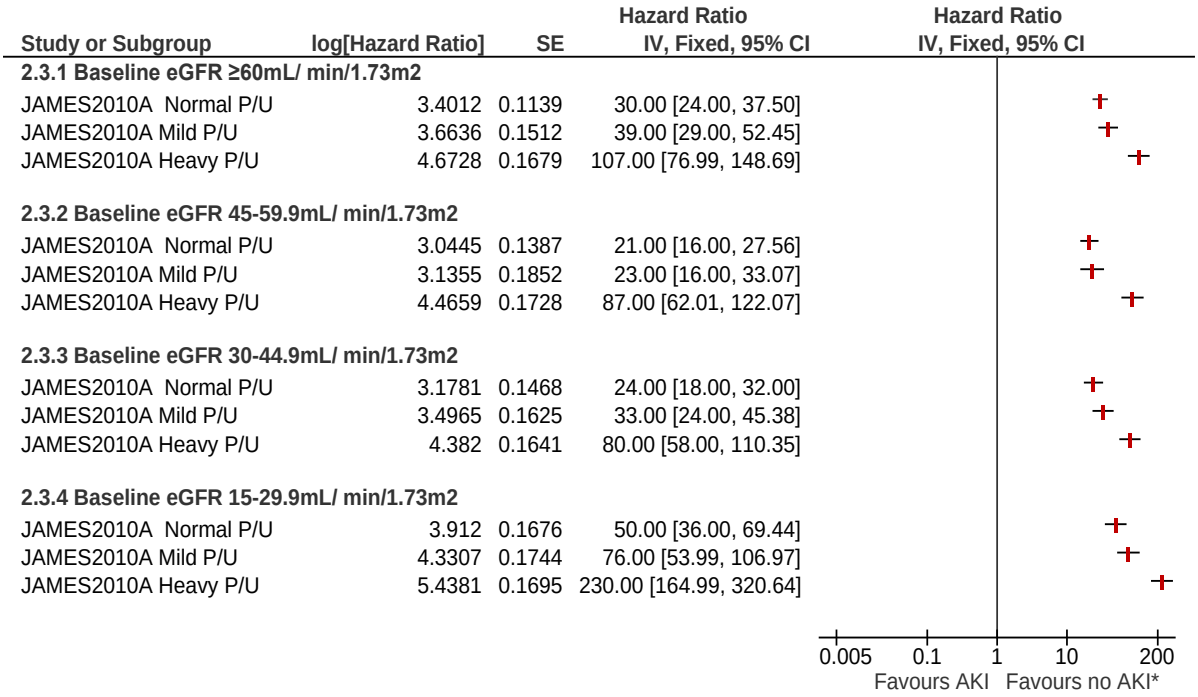


Figure 118: Risk of progression to CKD stage 4 or ESRD (composite outcome)



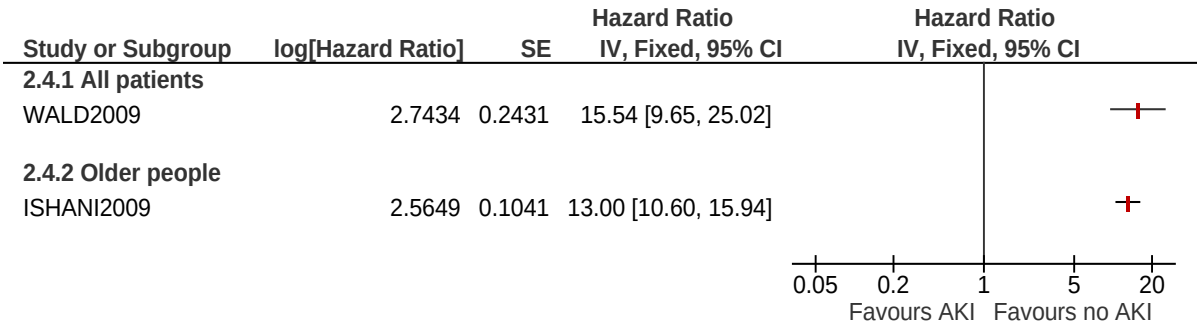
LO2009[395] only looked at dialysis requiring AKI and defined ESRD as CKD stage 5

Figure 119: Risk of ESRD or doubling of serum creatinine (*referent group = no AKI, normal proteinuria and eGFR≥60ml/ min/1.73m^2)



P/U=Proteinuria

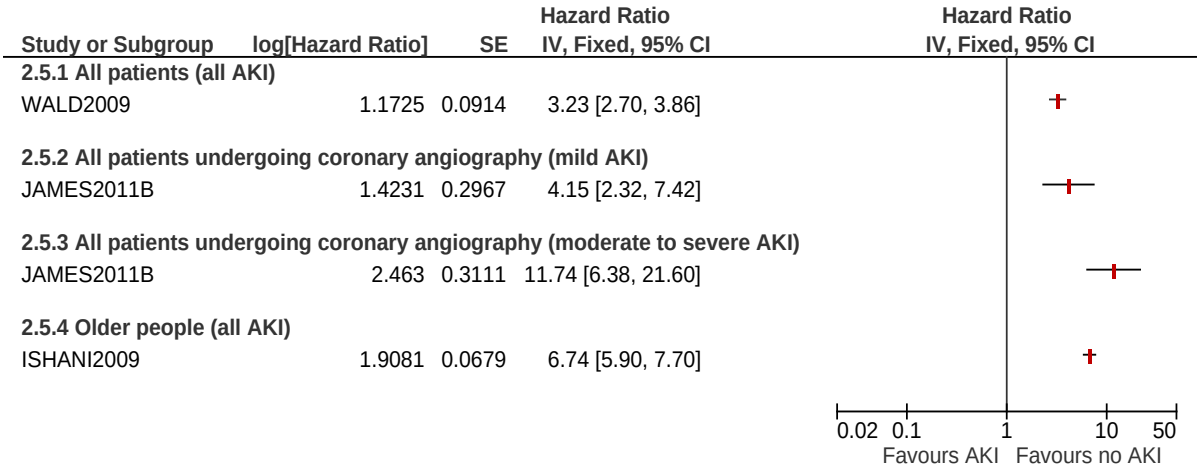
Figure 120: Risk of ESRD in people with no prior CKD



WALD2009[706] defined ESRD as chronic dialysis beginning .30 days after discharge and lasting ≥90 days. Mean age 62 years.

ISHANI2009[304] defined ESRD as enrolment in the ESRD program. Excluded people <67 years; mean age 79.2

Figure 121: Risk of ESRD in mixed population (CKD and no CKD) at baseline

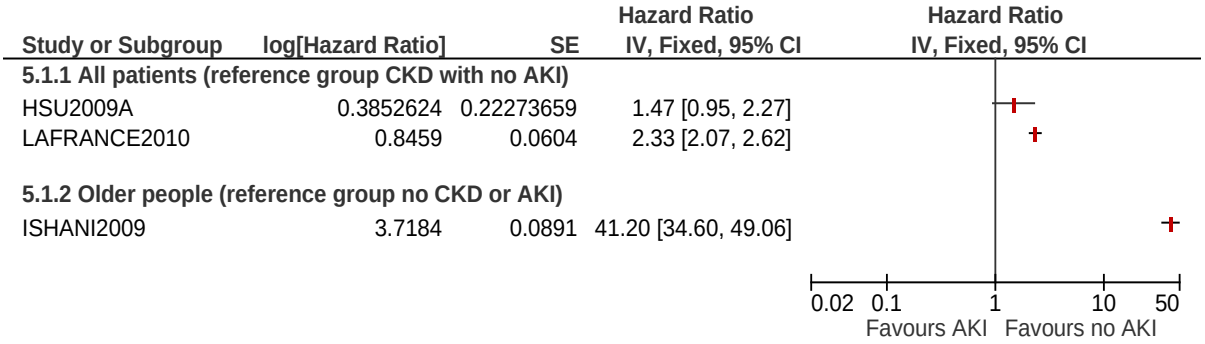


WALD2009[706] defined ESRD as chronic dialysis beginning .30 days after discharge and lasting ≥90 days. Mean age 62 years.

JAMES2011B[309] defined ESRD as dialysis dependence or renal transplant. Mean age no AKI=62.6 years; mild AKI=68.0 years; moderate to severe AKI= 67.4 years.

ISHANI2009[304] defined ESRD as enrolment in the ESRD program. Excluded people <67 years; mean age 79.2 years.

Figure 122: Risk of ESRD in people with CKD

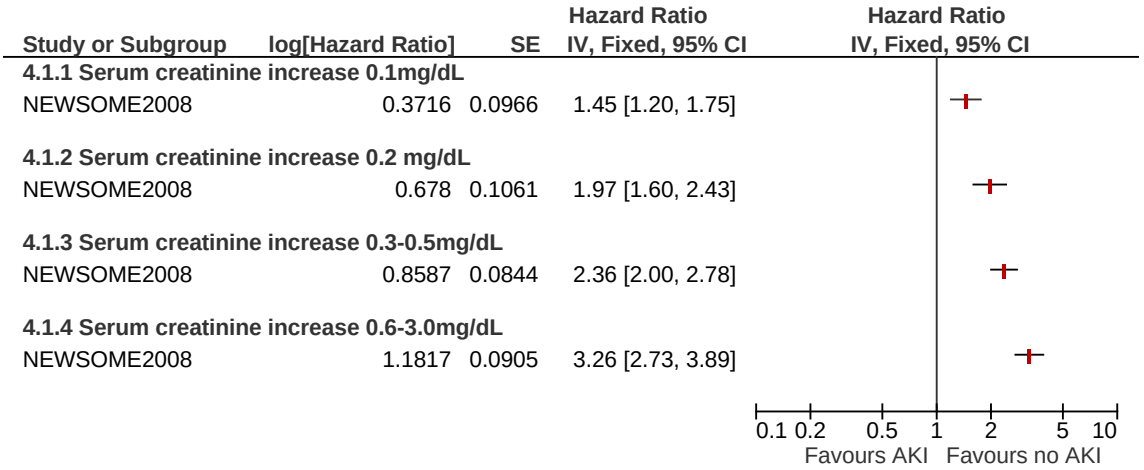


HSU2009[285] only looked at dialysis requiring AKI and defined ESRD as start of RRT in people who did not develop ESRD within 30 days of discharge. Mean age 66.6 years AKI group: 73.5 years in no AKI group.

LAFRANCE2010[366] defined ESRD as start of chronic dialysis initiation. Mean age 69.8

ISHANI2009[304] defined ESRD as enrolment in the ESRD program. Excluded people <67 years; mean age 79.2 years.

Figure 123: Risk of ESRD in older people after small increases in serum creatinine



I.7 Low protein diet

I.7.1 Low protein diet compared to higher protein diet in people with CKD

Figure 124: Progression of CKD (measured by end stage renal disease requiring RRT) (Hazard ratios)

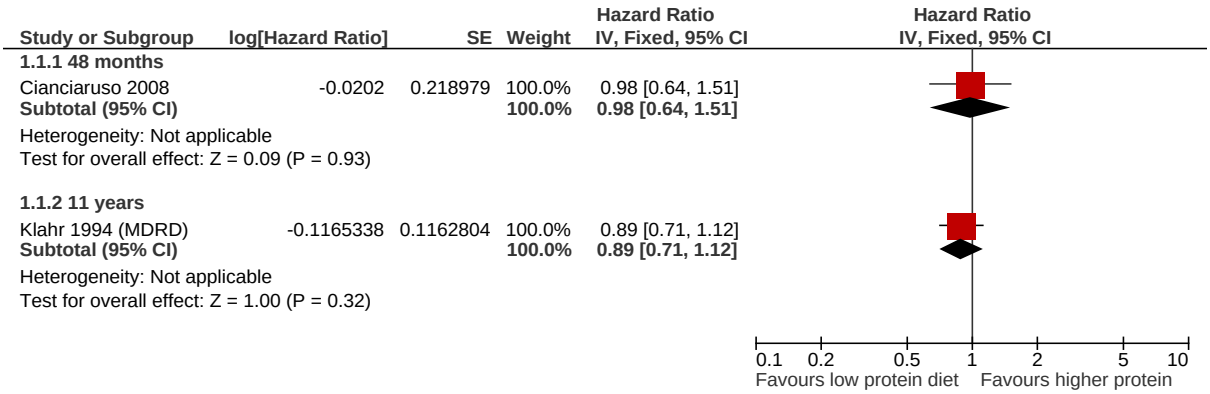


Figure 125: Progression of CKD (measured by end stage renal disease requiring RRT)

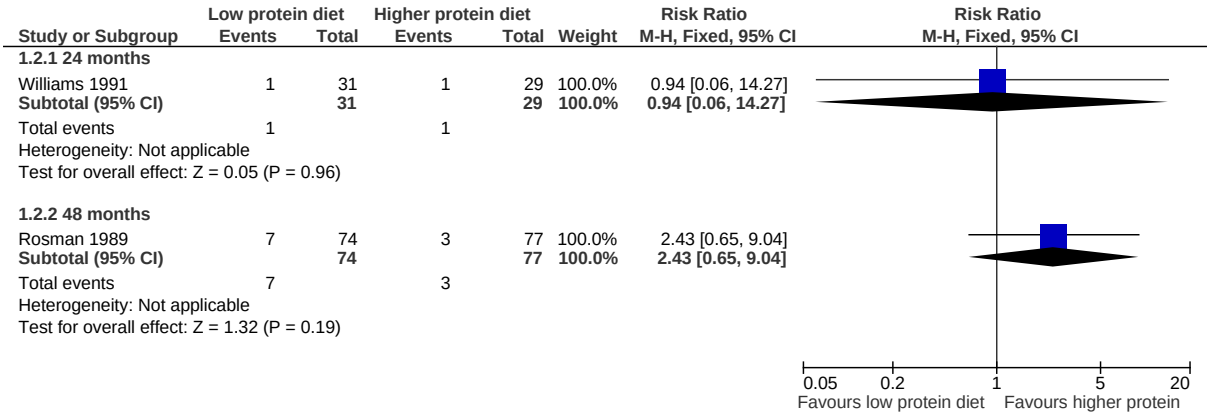


Figure 126: Progression of CKD (measured by change in GFR)

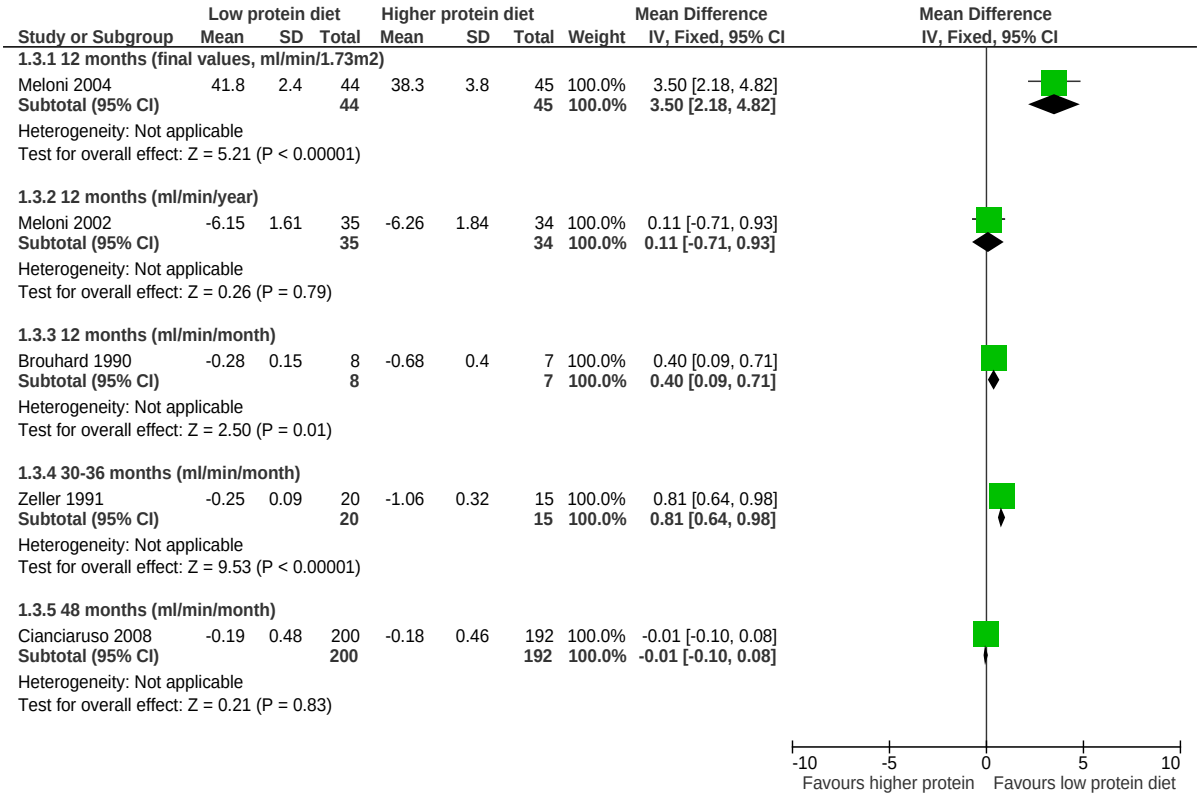


Figure 127: Mortality (all-cause and cardiovascular) (Hazard ratios)

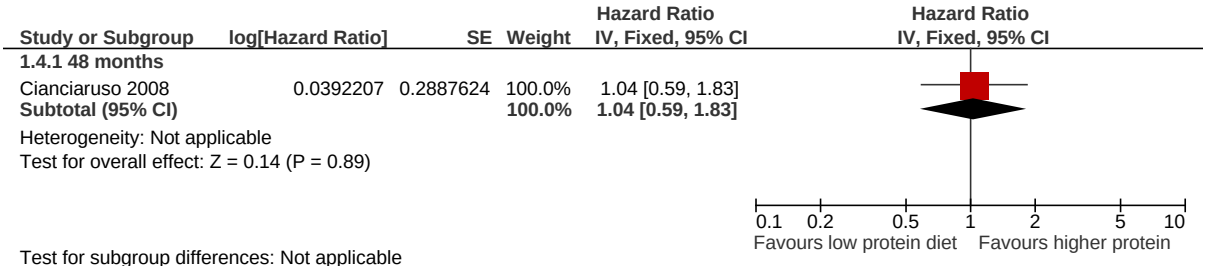


Figure 128: Mortality (all-cause and cardiovascular)

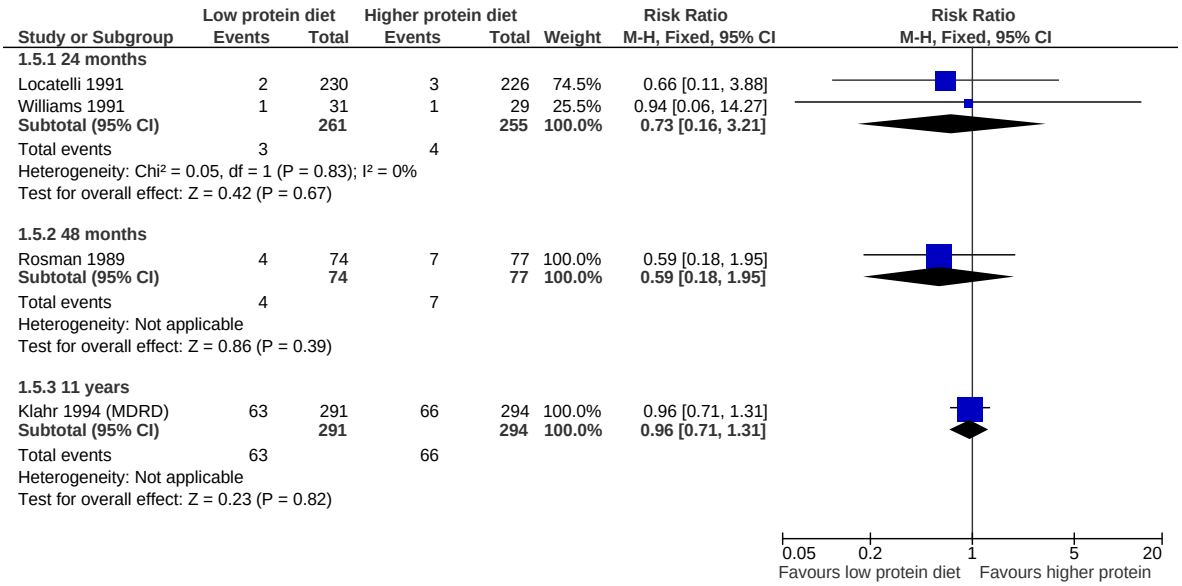


Figure 129: Compliance (measured by actual protein intake) 12-18 months

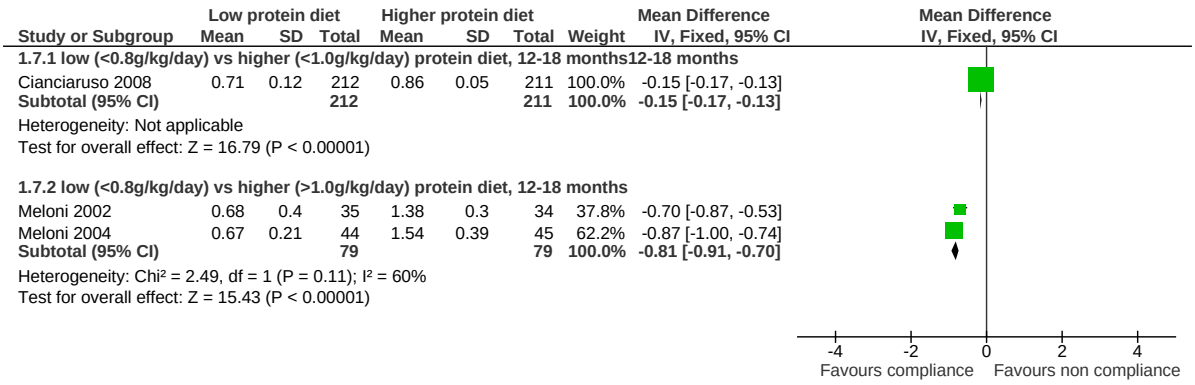


Figure 130: Compliance (measured by actual protein intake) – 18-36 months

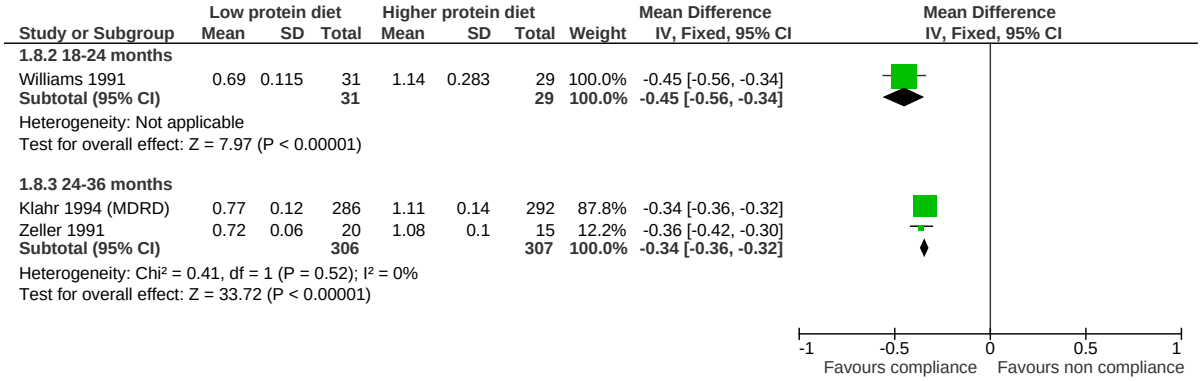


Figure 131: Nutritional status (measured by change in BMI)

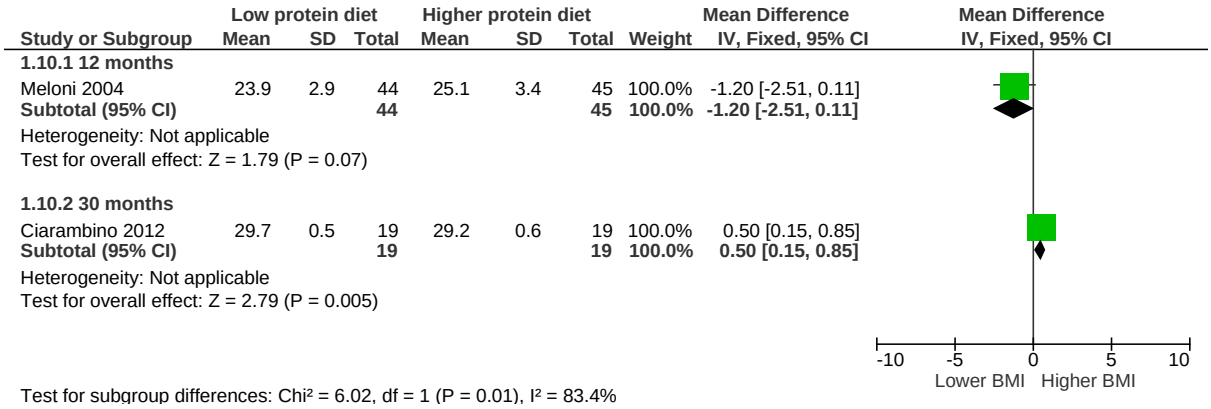
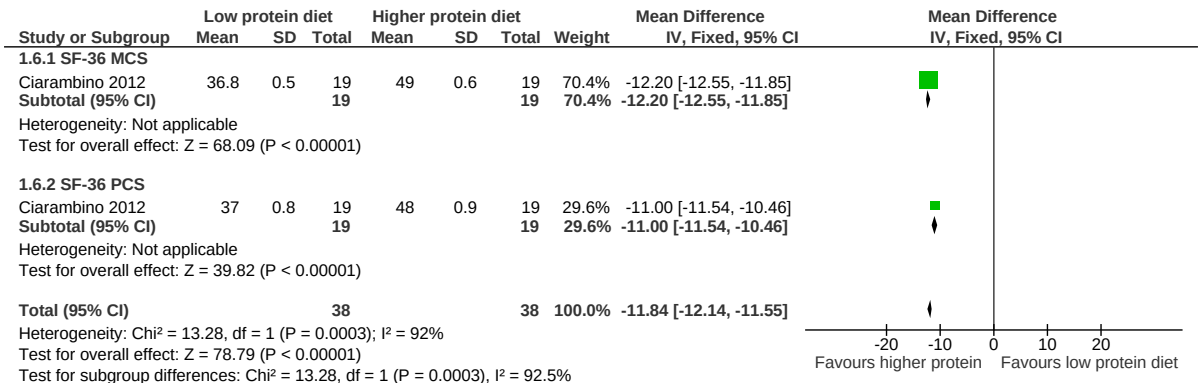


Figure 11: Health related quality of life



I.8 Self-management

I.8.1 Self-management support systems

Figure 132: Progression of CKD (eGFR)

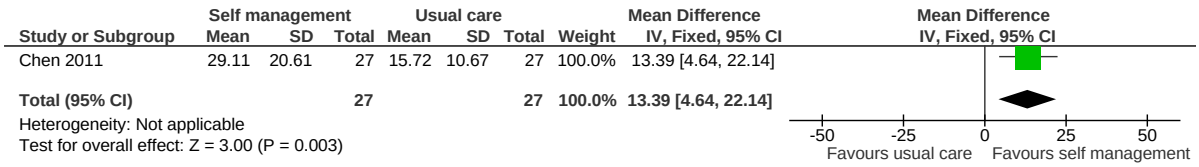


Figure 133: Dialysis

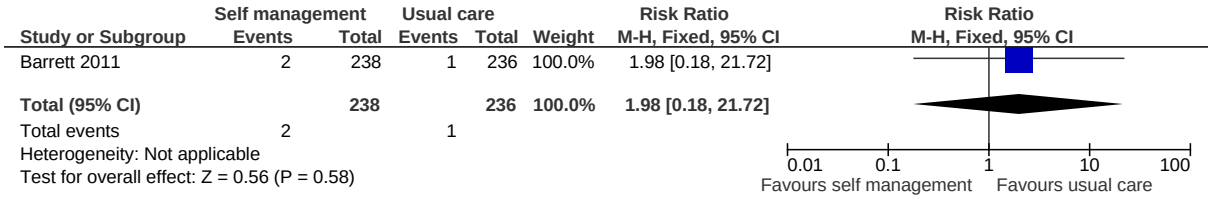


Figure 134: Mortality all cause

Figure 135: Mortality cardiovascular

Study or Subgroup	Self management Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barrett 2011	2	238	2	236	100.0%	0.99 [0.14, 6.98]
Total (95% CI)		**238**		**236**	**100.0%**	**0.99 [0.14, 6.98]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

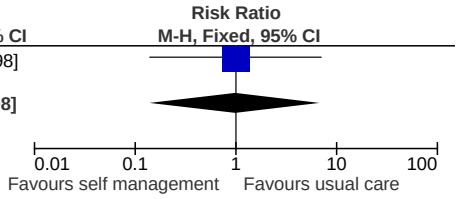


Figure 136: Hospitalisation all cause

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	5	27	12	27	100.0%	0.42 [0.17, 1.02]
Total (95% CI)		**27**		**27**	**100.0%**	**0.42 [0.17, 1.02]**
Total events	5		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

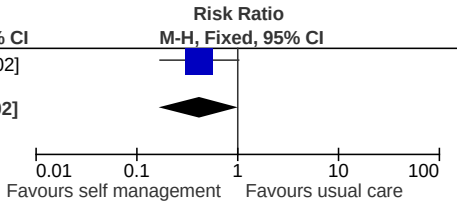
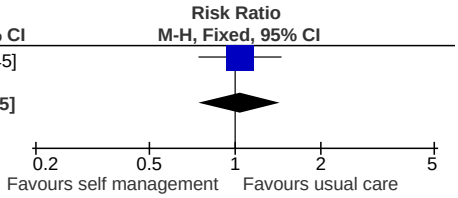


Figure 137: Adherence to treatments

Study or Subgroup	Self management Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Williams 2012	24	36	25	39	100.0%	1.04 [0.75, 1.45]
Total (95% CI)		**36**		**39**	**100.0%**	**1.04 [0.75, 1.45]**
Total events	24		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



I.9 Blood pressure – combined renin-angiotensin-aldosterone system antagonists

I.9.1 ACE inhibitors versus placebo

I.9.1.1 Progression of CKD – measured by change in eGFR

Figure 138: ACE inhibitor vs.placebo in people with CKD and diabetes – Hazard ratio

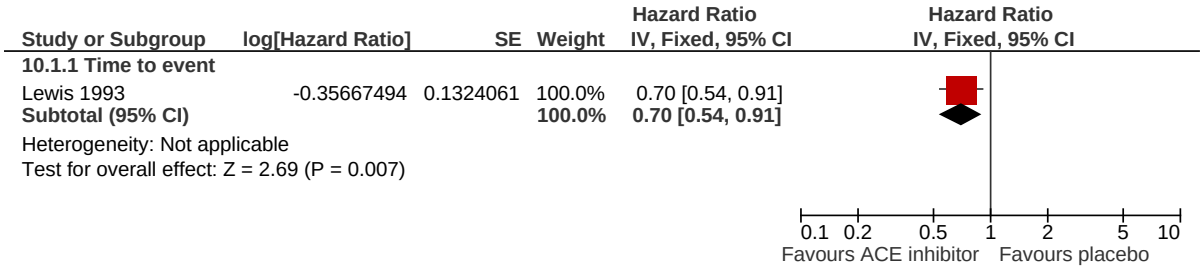
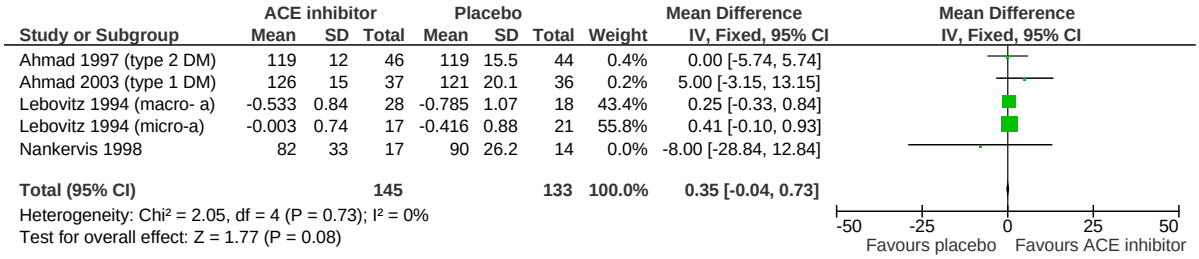


Figure 139: ACE inhibitor vs.placebo in people with CKD and diabetes - Mean difference



I.9.1.2 Progression of CKD – Occurrence of end stage renal disease

Figure 140: ACE inhibitor vs.placebo in people with non-diabetic CKD– Hazard ratio

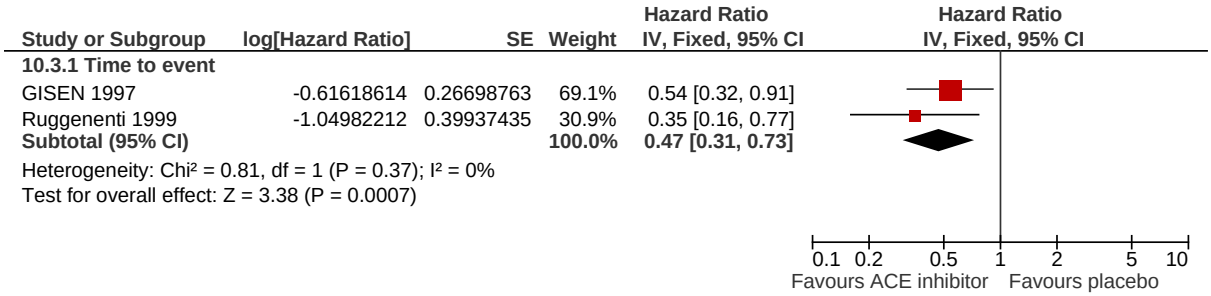
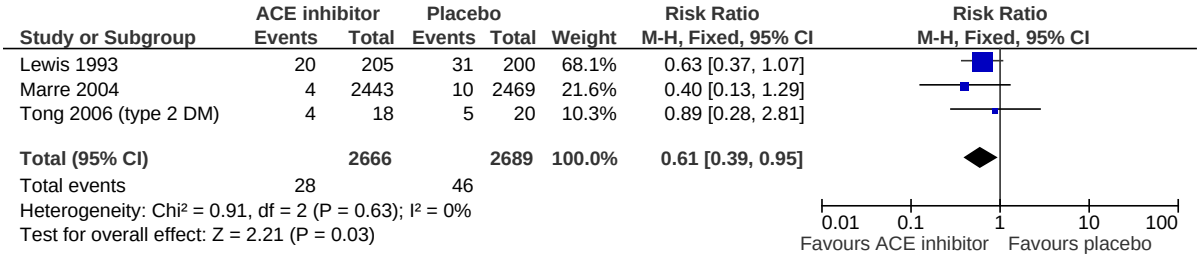


Figure 141: ACE inhibitor vs.placebo in people with CKD and diabetes - Relative risk



I.9.1.3 All-cause mortality

Figure 142: ACE inhibitor vs.placebo in people with CKD (mixed population with and without diabetes) – Hazard ratio

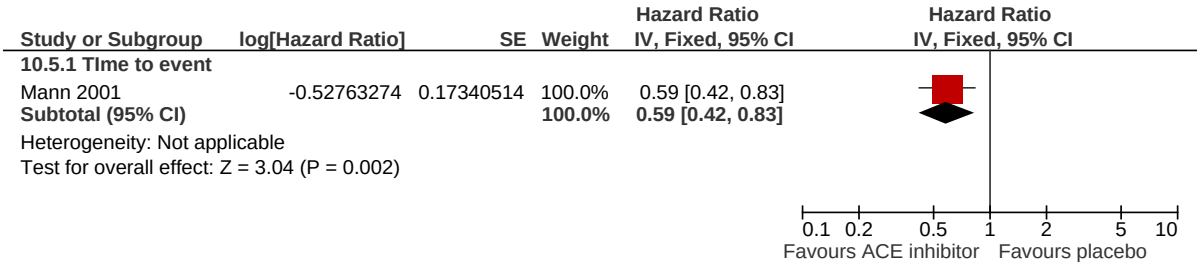
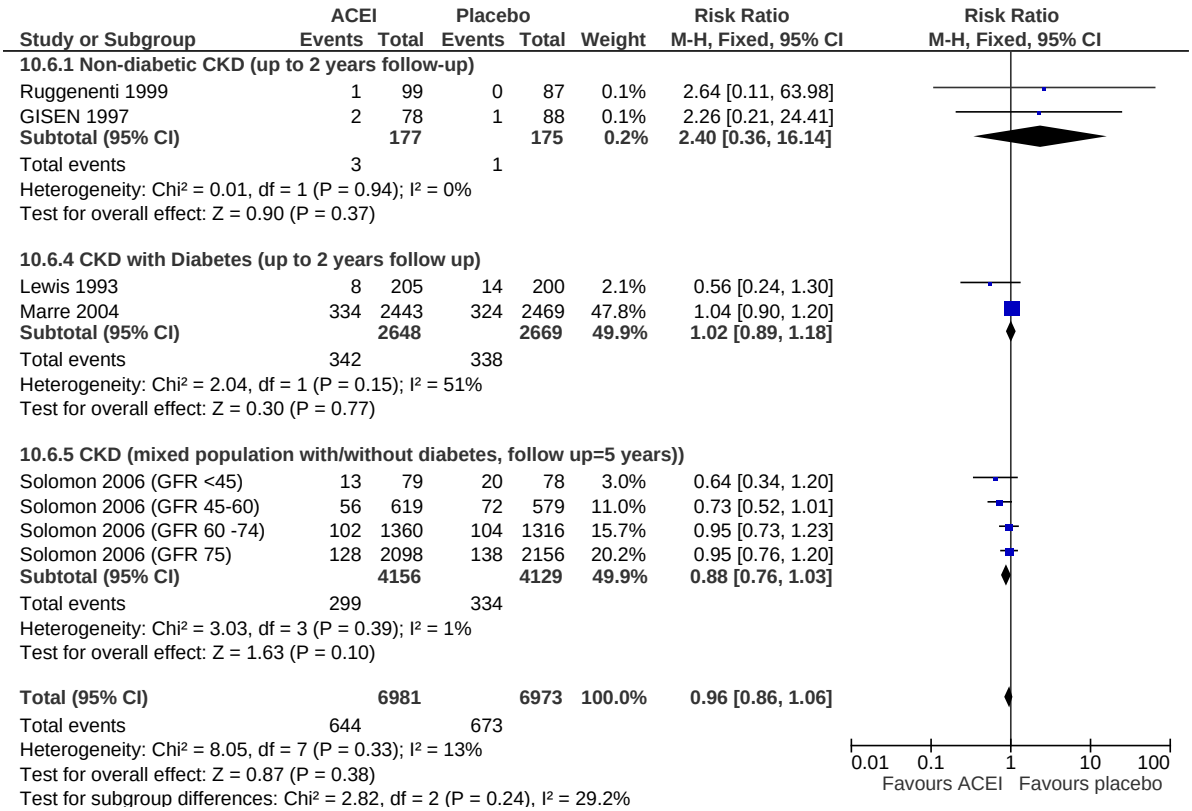


Figure 143: ACE inhibitor vs.placebo in people with CKD - Relative risk



I.9.1.4 Cardiovascular mortality

Figure 144: ACE inhibitor vs.placebo in people with CKD (with or without diabetes) – Hazard ratio

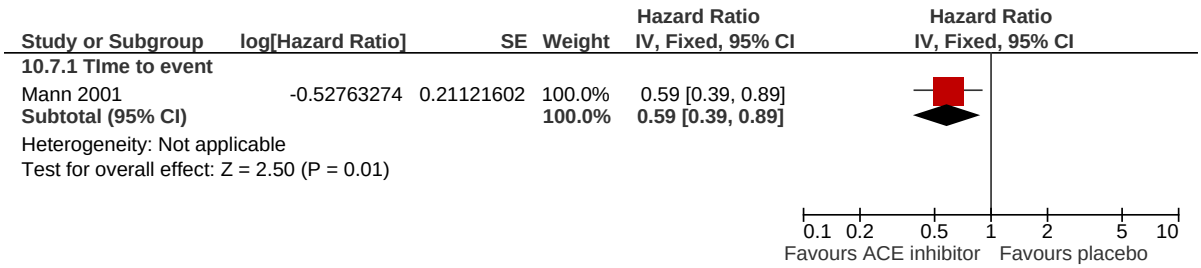
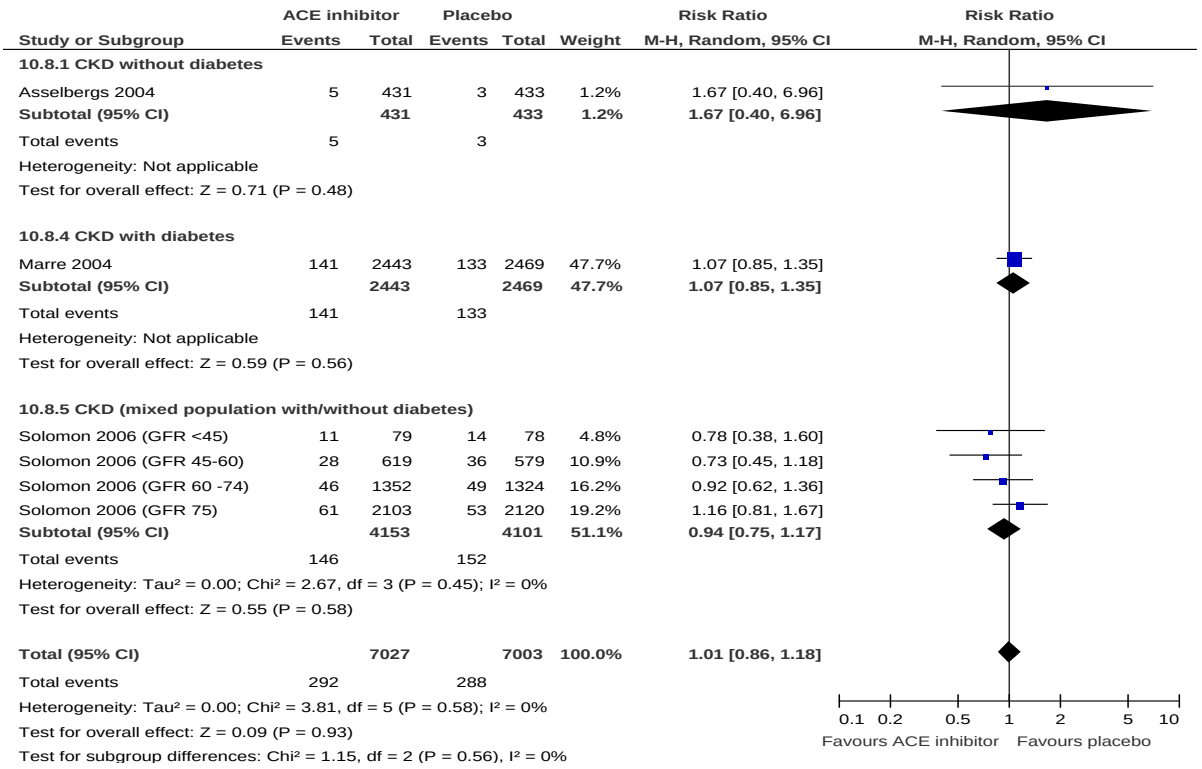


Figure 145: ACE inhibitor vs.placebo in people with CKD - Relative risk



I.9.1.5 Cardiovascular events

Figure 146: ACE inhibitor vs.placebo in people with non-diabetic CKD - Hazard ratio

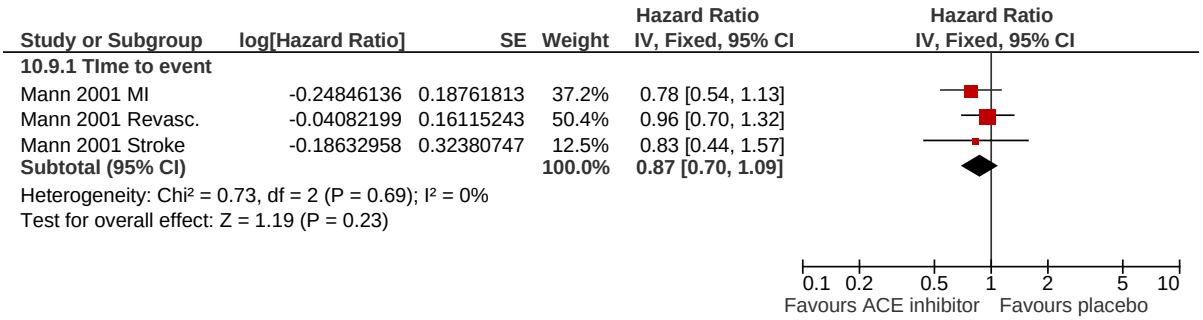
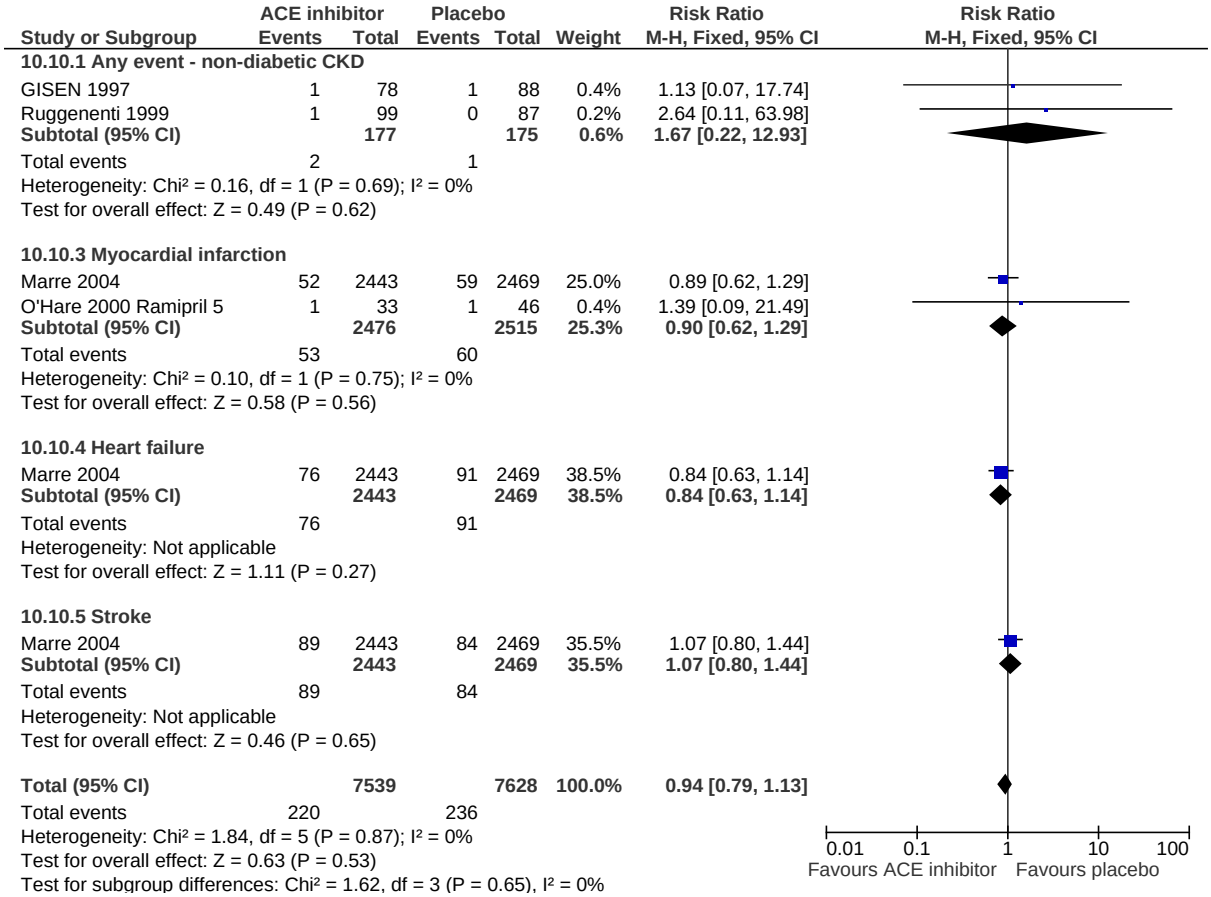


Figure 147: ACE inhibitor vs.placebo in people with CKD (with diabetes unless stated) - Relative risk



I.9.1.6 Change in proteinuria

Progression to clinical proteinuria

Figure 148: ACE inhibitor vs.placebo in people with CKD and diabetes - Hazard ratio

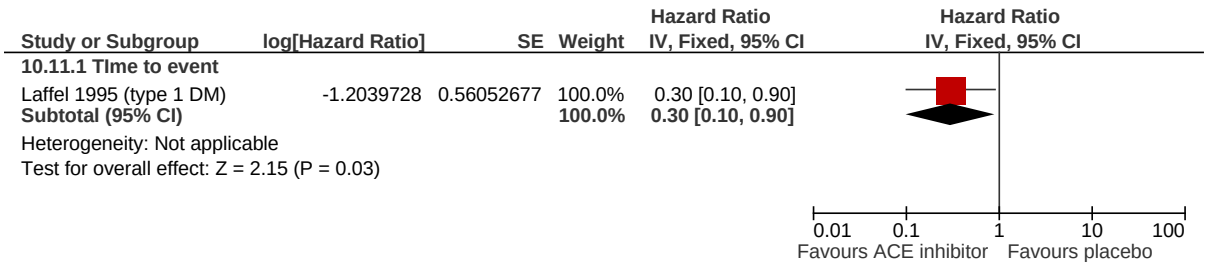
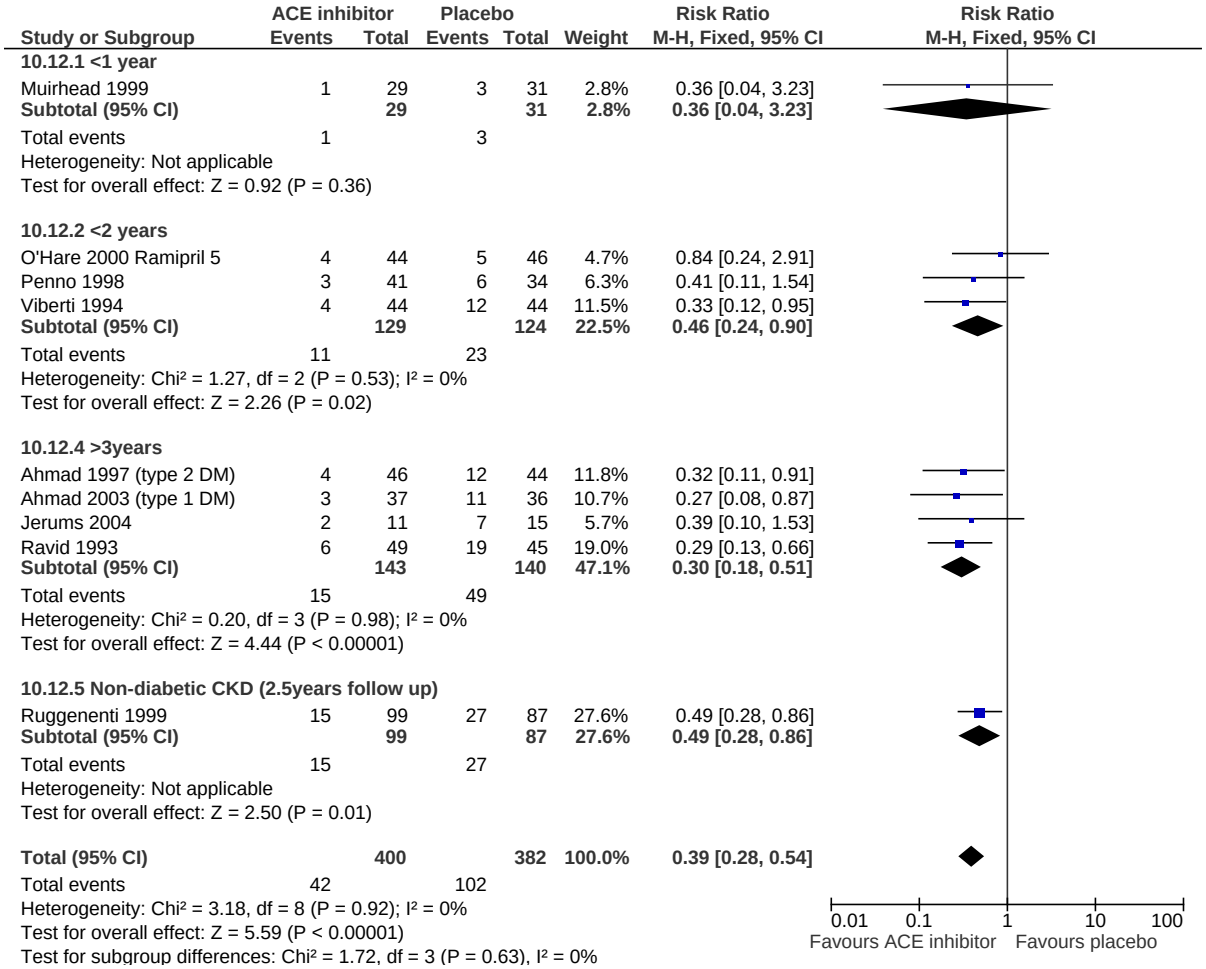
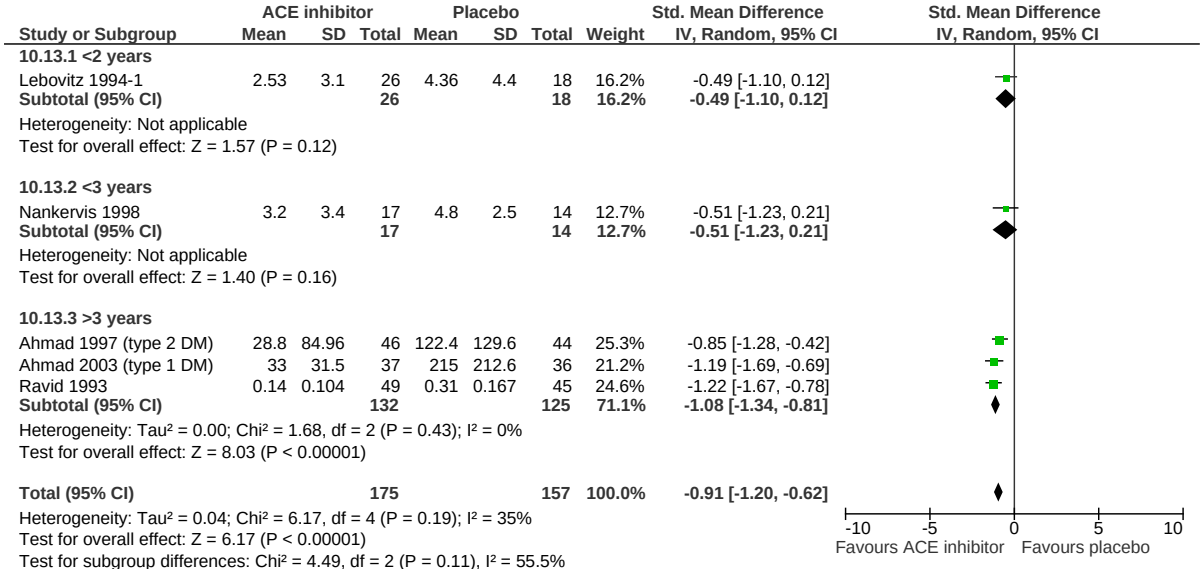


Figure 149: ACE inhibitor vs.placebo in people with CKD (with diabetes unless stated) - Relative risk



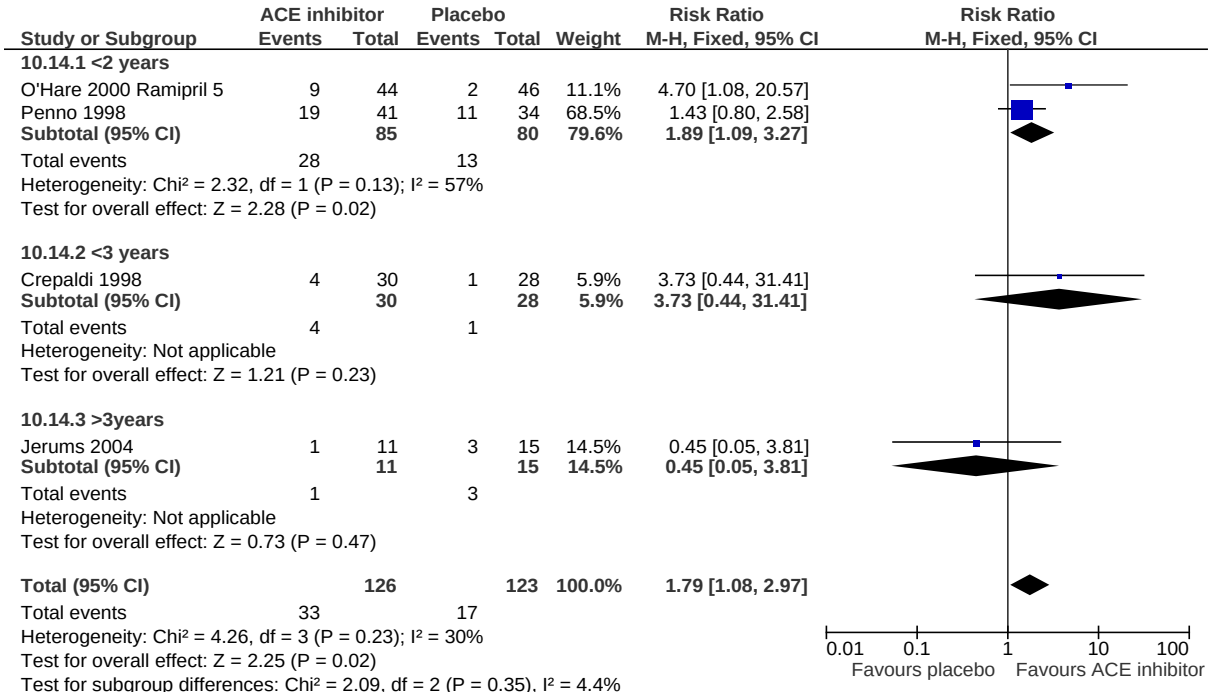
Albumin excretion rate / 24hours

Figure 150: ACE inhibitor vs.placebo in people with CKD and diabetes - Standardised mean difference



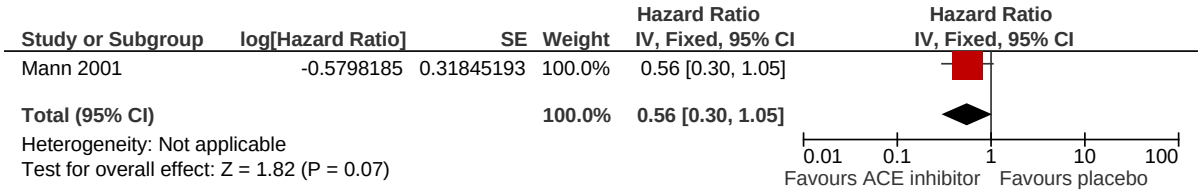
I.9.1.7 Regression to normoalbuminuria

Figure 151: ACE inhibitor vs.placebo in people with CKD and diabetes - Relative risk



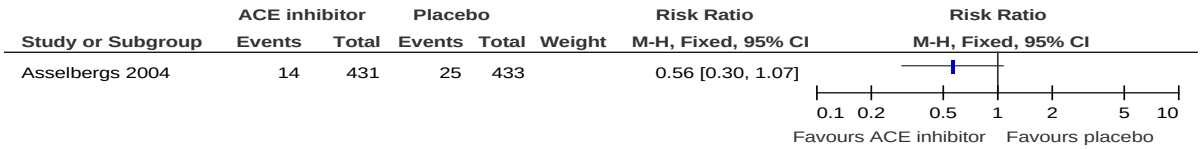
I.9.1.8 Hospitalisation (due to heart failure)

Figure 152: ACE inhibitor vs.placebo in people with CKD (with and without diabetes) - Hazard ratio



I.9.1.9 Hospitalisation (for non-fatal myocardial infarction, heart failure, peripheral vascular disease or cerebrovascular accident).

Figure 153: ACE inhibitor vs.placebo in people with CKD (without diabetes)



I.9.2 ARB versus placebo

I.9.2.1 Progression of CKD – measured by change in eGFR

Figure 154: ARB vs.placebo in people with CKD and diabetes - Hazard ratio

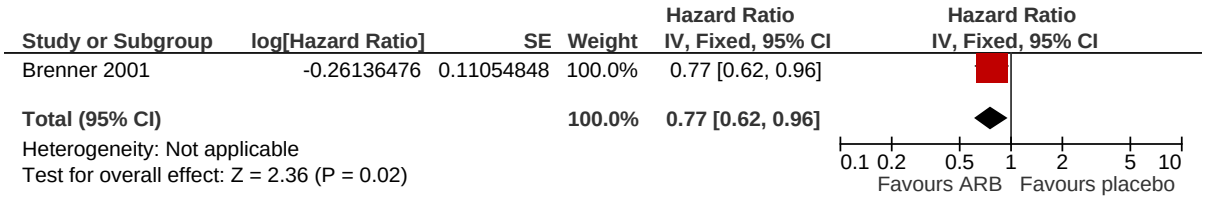
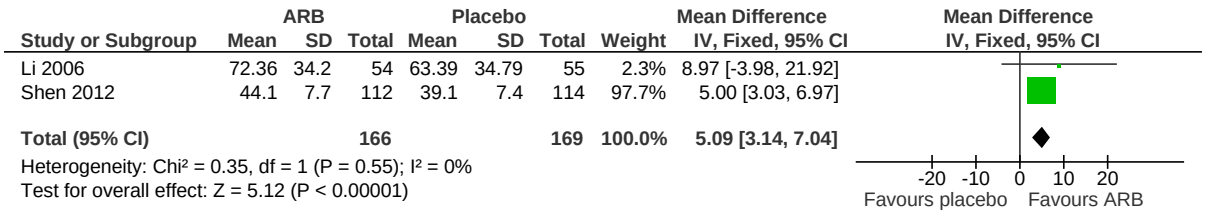
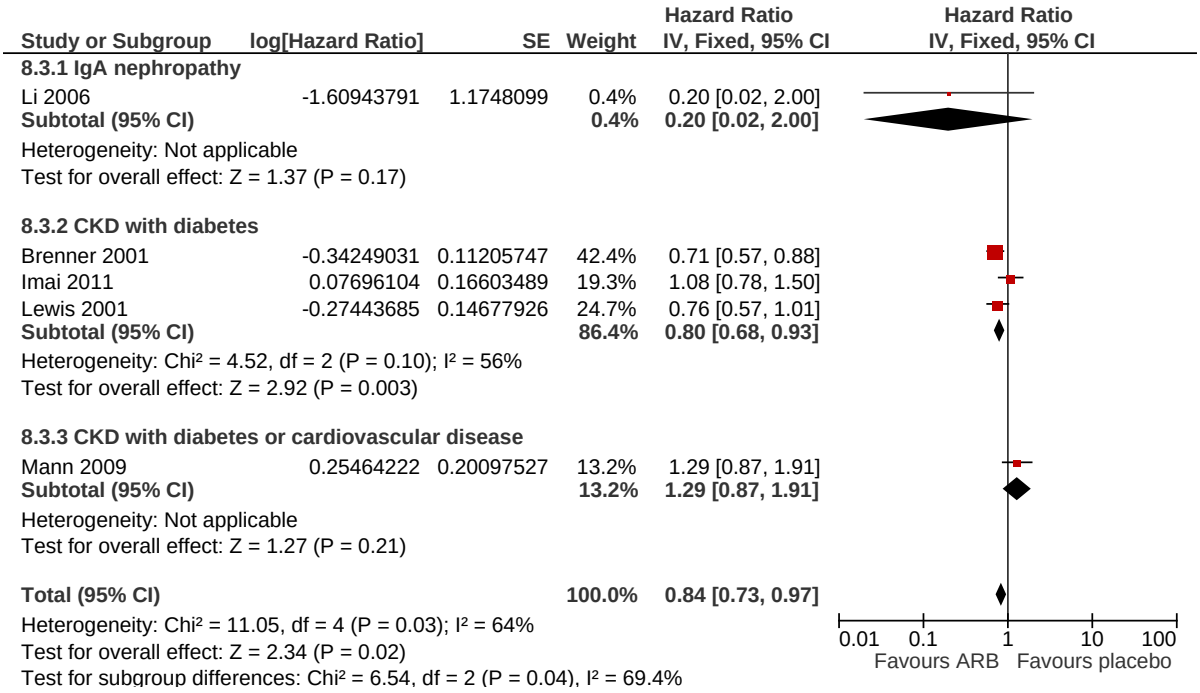


Figure 155: ARB vs.placebo in people with non-diabetic CKD - Mean difference



I.9.2.2 Progression of CKD – Occurrence of end stage renal disease

Figure 156: ARB vs.placebo in people with CKD (with and without diabetes) - Hazard ratio



I.9.2.3 All-cause mortality

Figure 157: ARB vs.placebo in people with CKD (with and without diabetes) - Hazard ratio

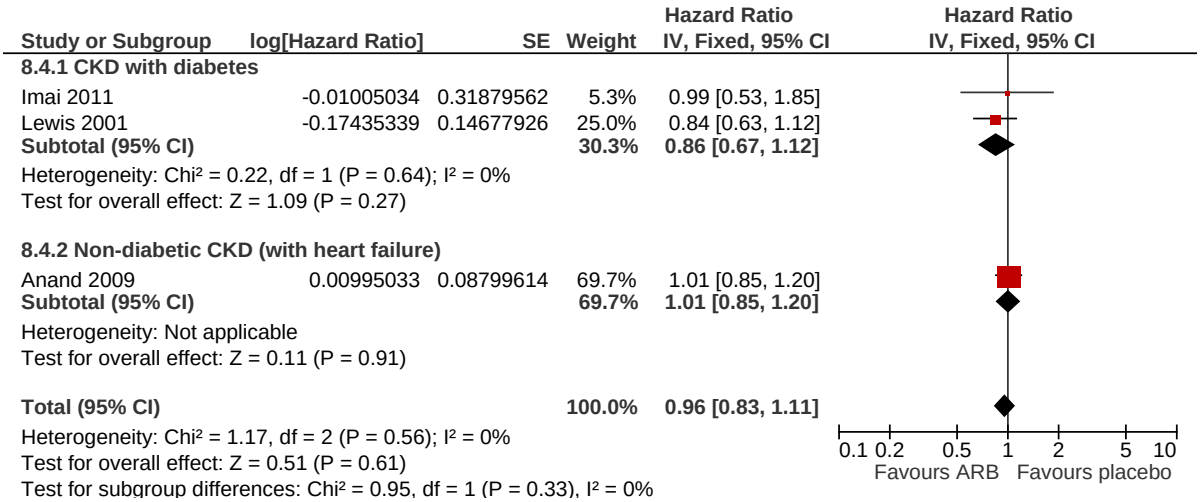
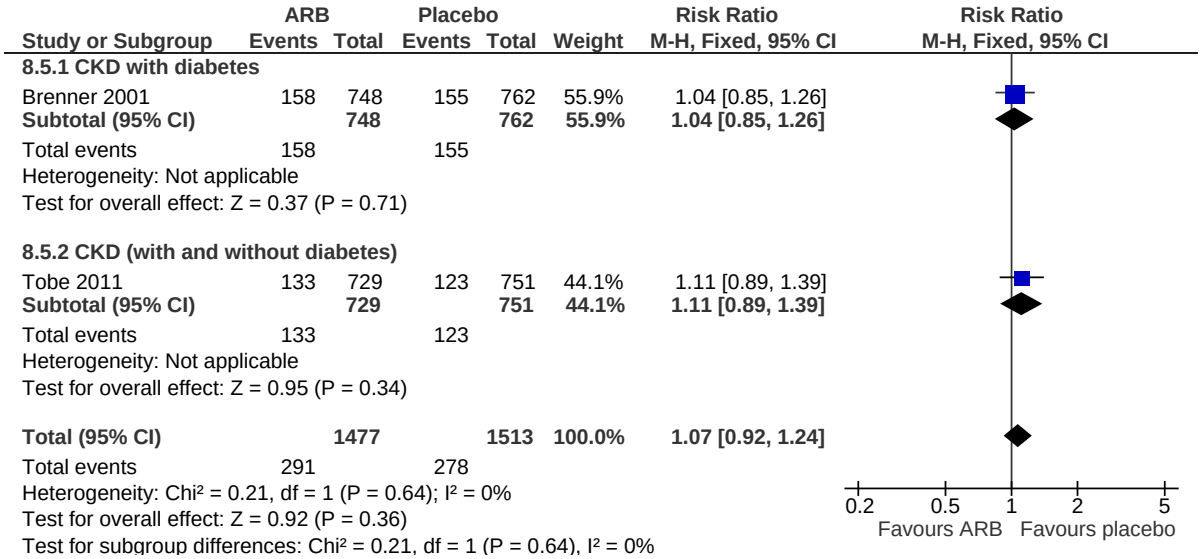


Figure 158: ARB vs.placebo in people with CKD (with and without diabetes) - Relative risk



I.9.2.4 Cardiovascular mortality

Figure 159: ARB vs.placebo in people with CKD and diabetes - Hazard ratio

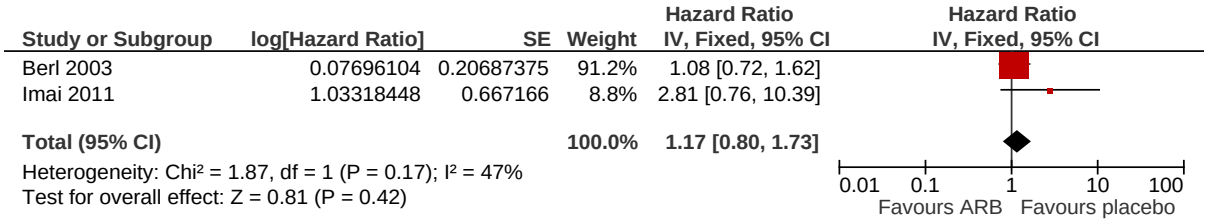
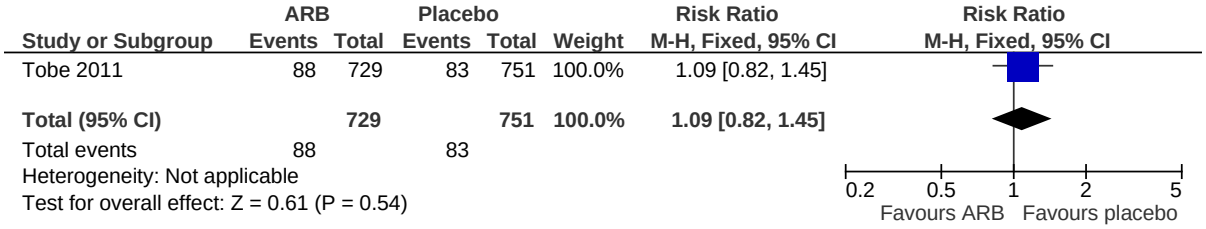


Figure 160: ARB vs.placebo in people with CKD (with and without diabetes) - Relative risk



I.9.2.5 Cardiovascular events

Figure 161: ARB vs.placebo in people with CKD and diabetes - Hazard ratio

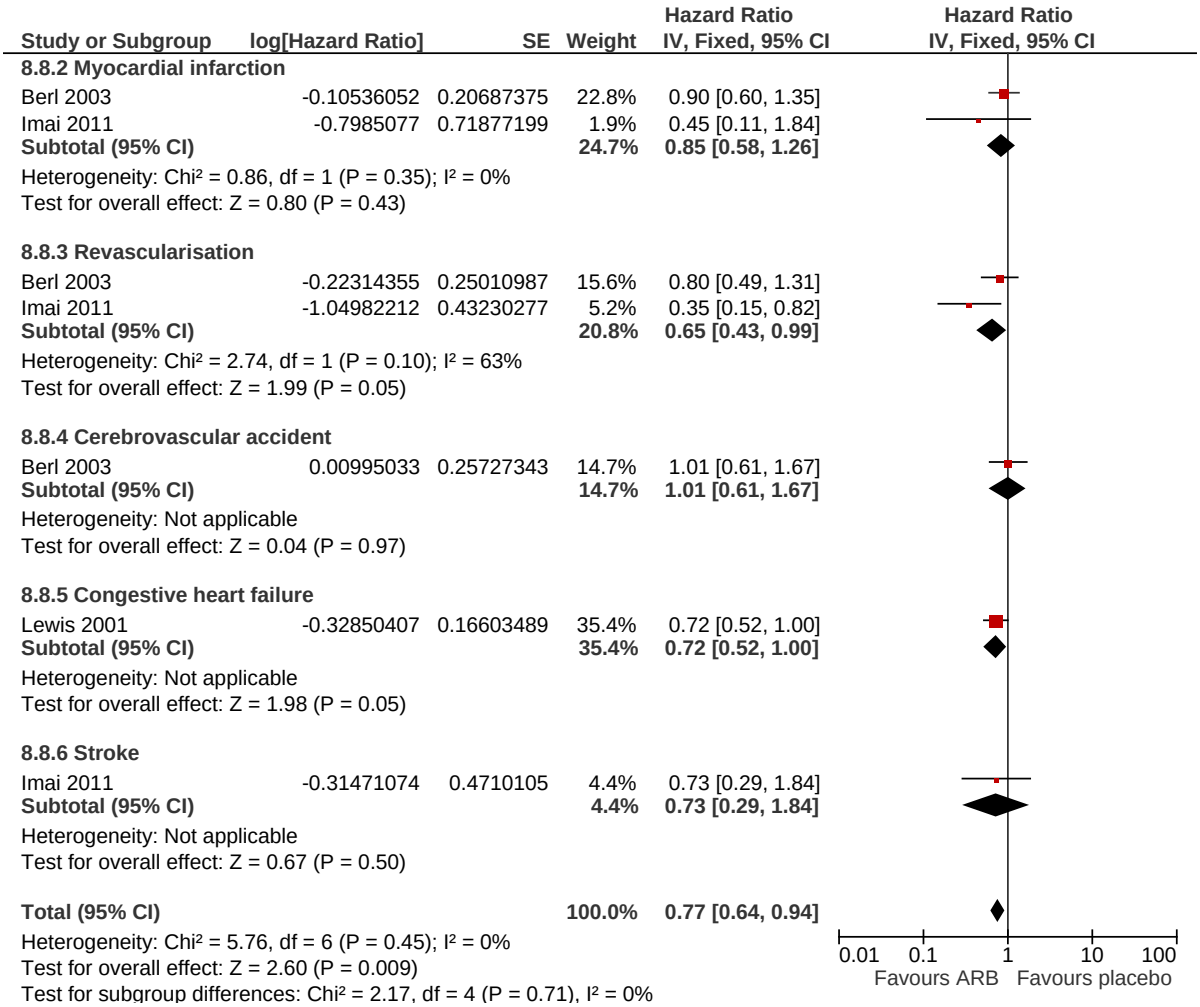
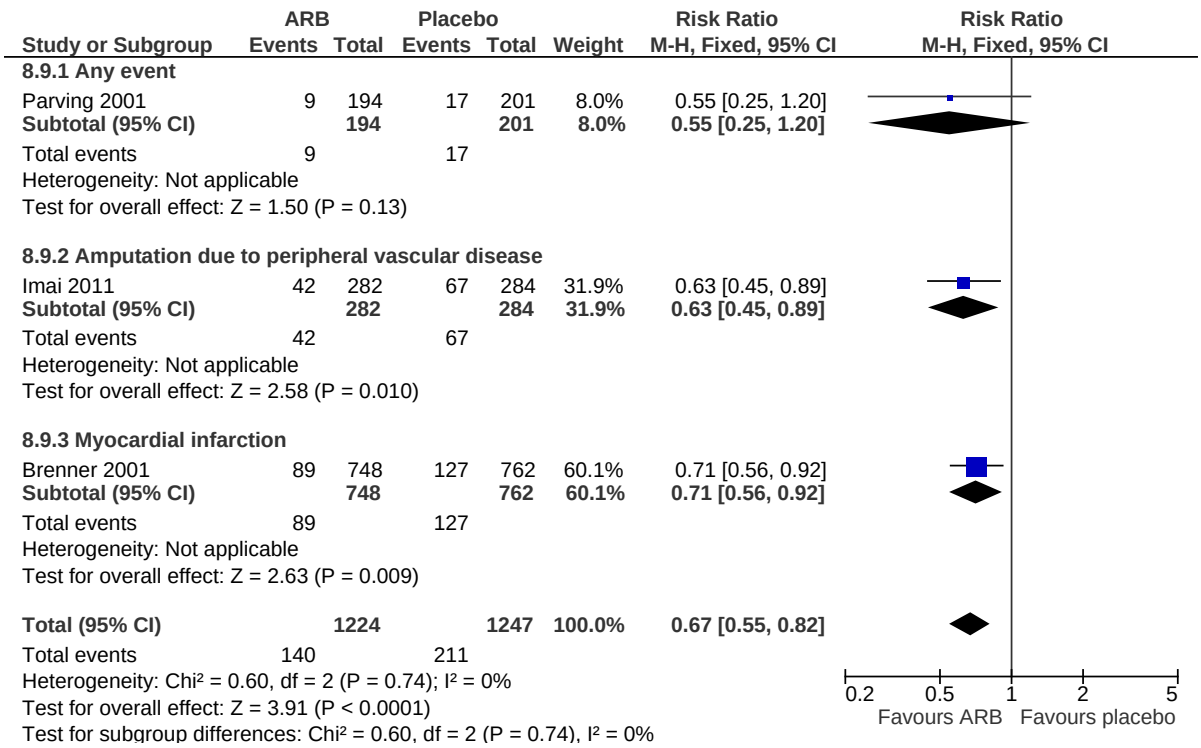
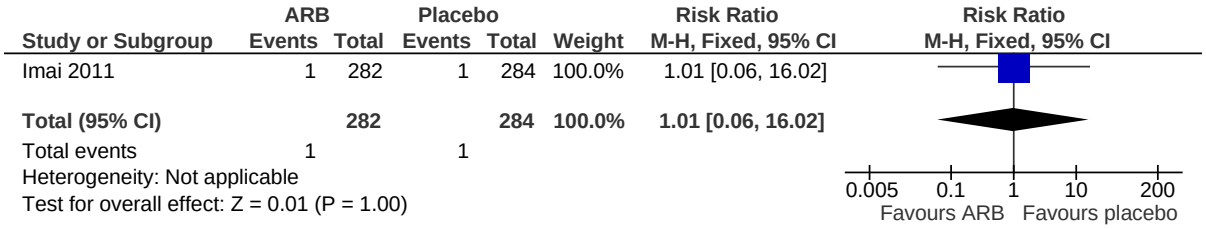


Figure 162: ARB vs.placebo in people with CKD and diabetes - Relative risk



I.9.2.6 Occurrence of AKI

Figure 163: ARB vs.placebo in people with CKD and diabetes - Relative risk



I.9.2.7 Change in proteinuria

Figure 164: ARB vs.placebo in people with CKD and diabetes (unless stated) – progression to clinical proteinuria, macroalbuminuria or overt nephropathy

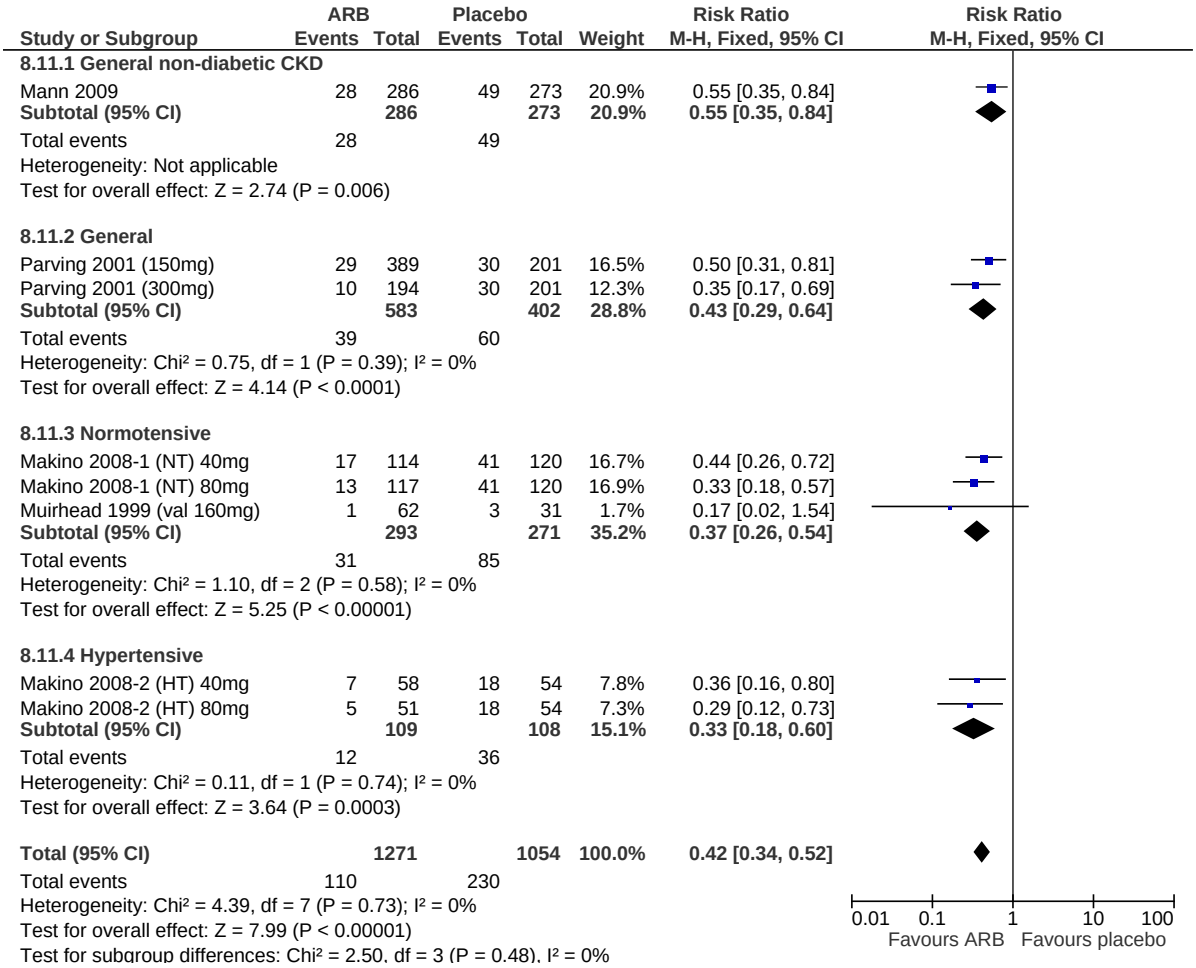


Figure 165: ARB vs.placebo in people with CKD (with and without diabetes) –final values

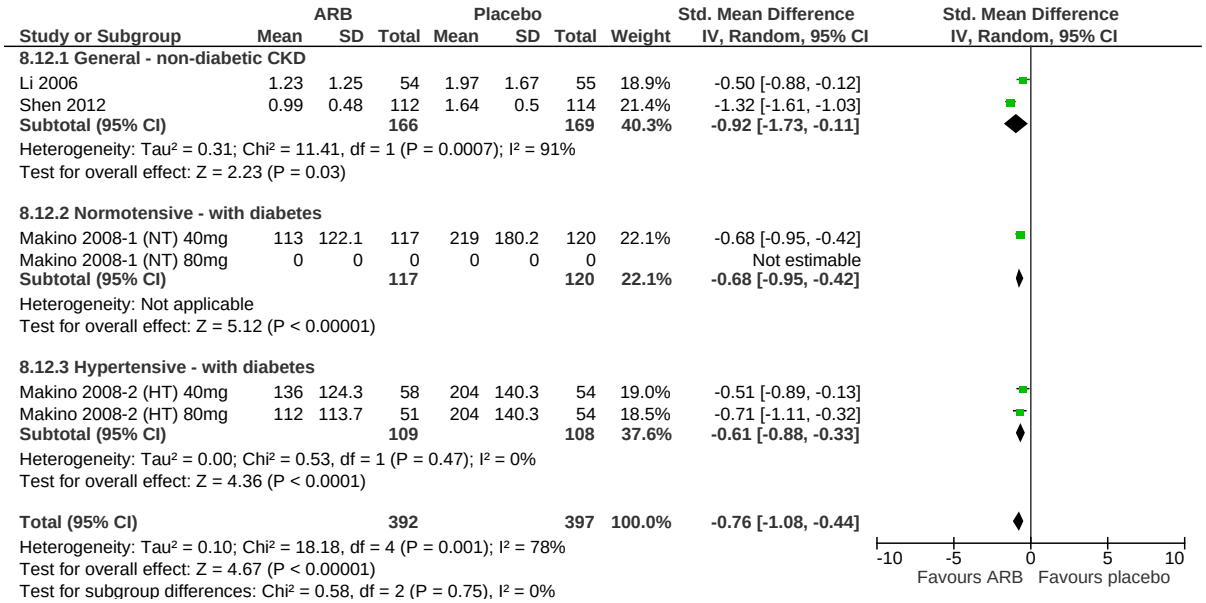
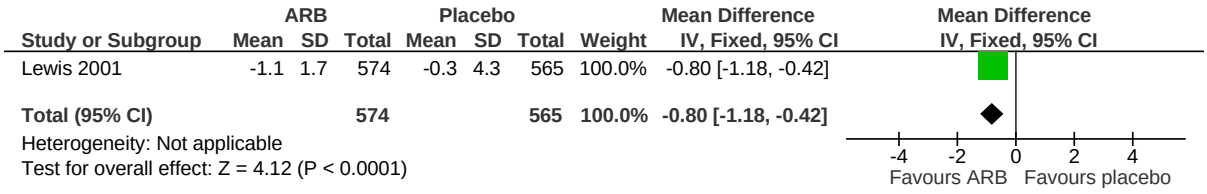
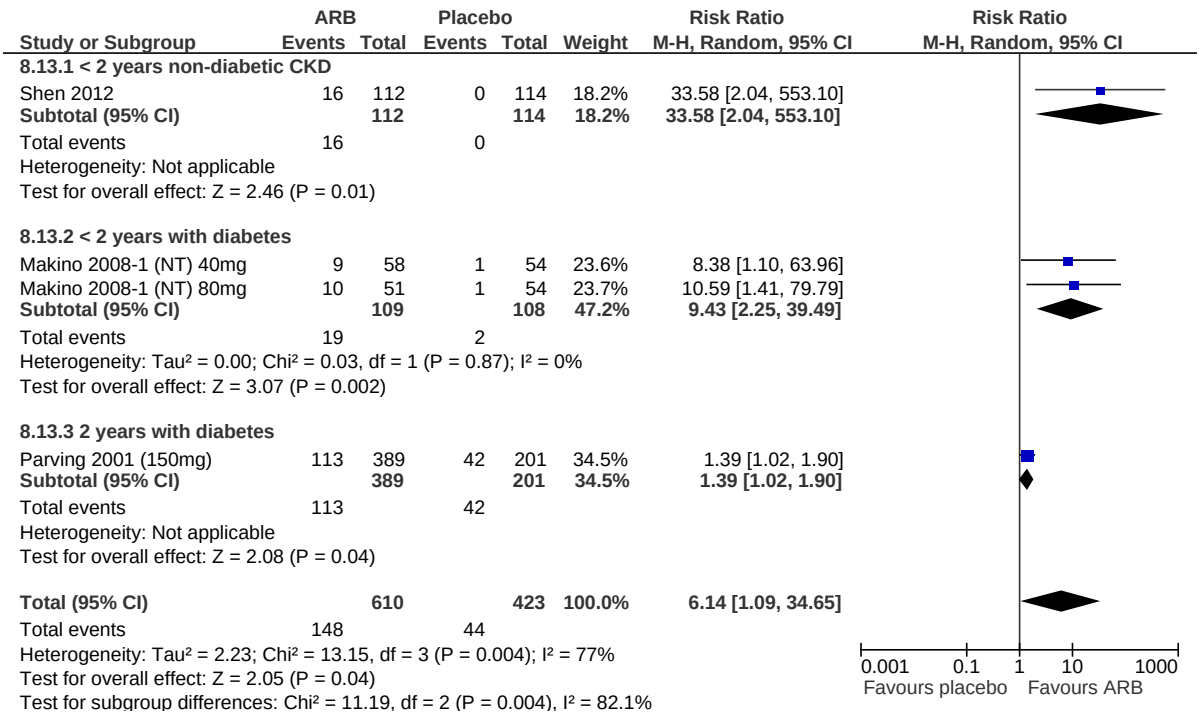


Figure 166: ARB vs.placebo in people with CKD and diabetes – change scores



I.9.2.8 Regression to normoalbuminuria

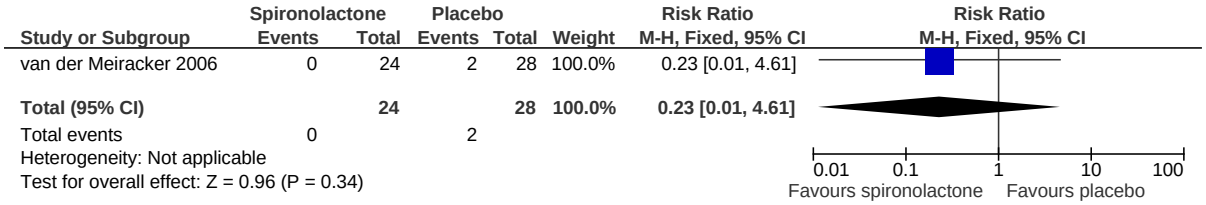
Figure 167: ARB vs.placebo in people with CKD and diabetes



I.9.3 Spironolactone versus placebo

I.9.3.1 All-cause mortality

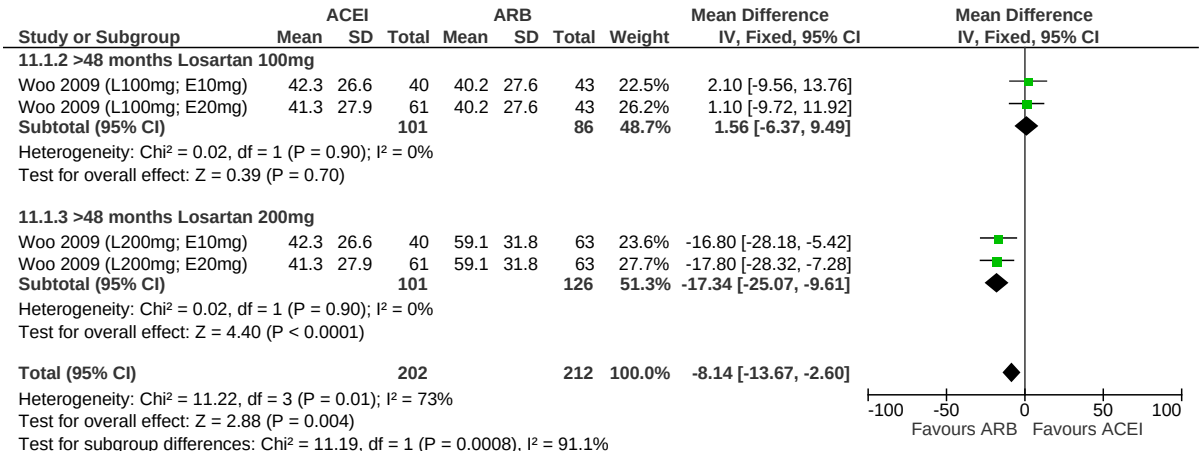
Figure 168: Spirinolactone vs.placebo in people with CKD and diabetes



I.9.4 ACE inhibitor versus ARB

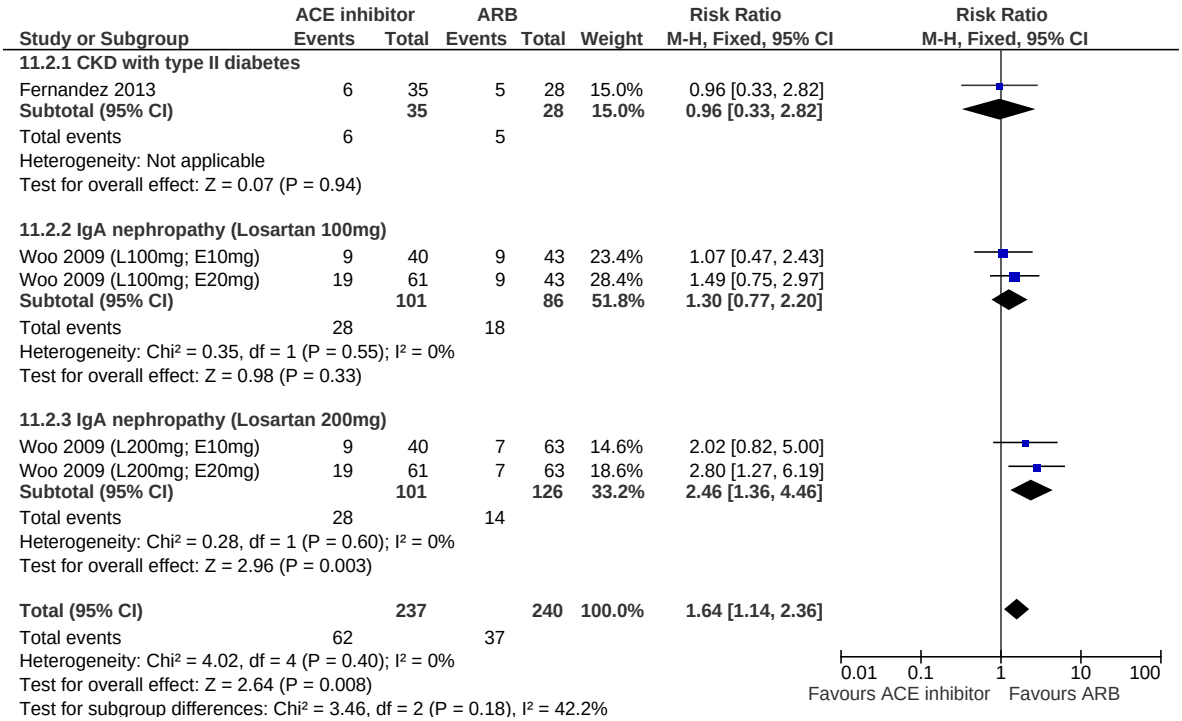
I.9.4.1 Progression of CKD – measured by change in eGFR

Figure 169: ACE inhibitor vs.ARB in people with non-diabetic CKD (IgA nephropathy)



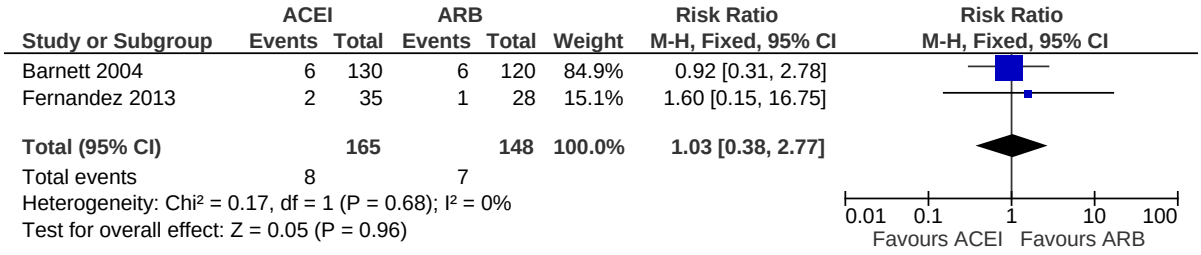
I.9.4.2 Progression of CKD – Occurrence of end stage renal disease

Figure 170: ACE inhibitor vs.ARB in people with CKD



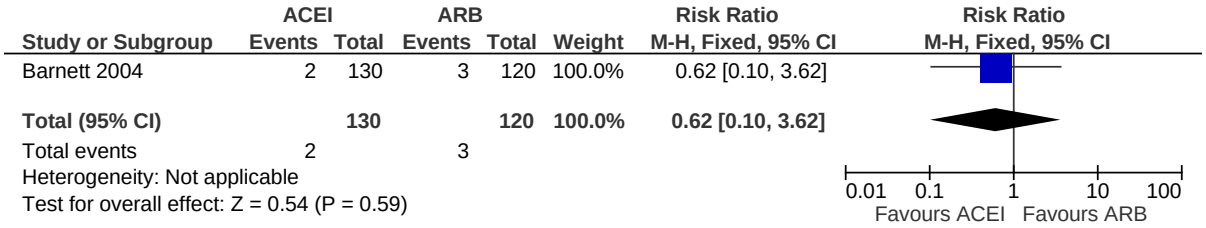
I.9.4.3 All-cause mortality

Figure 171: ACE inhibitor vs.ARB in people with CKD and diabetes



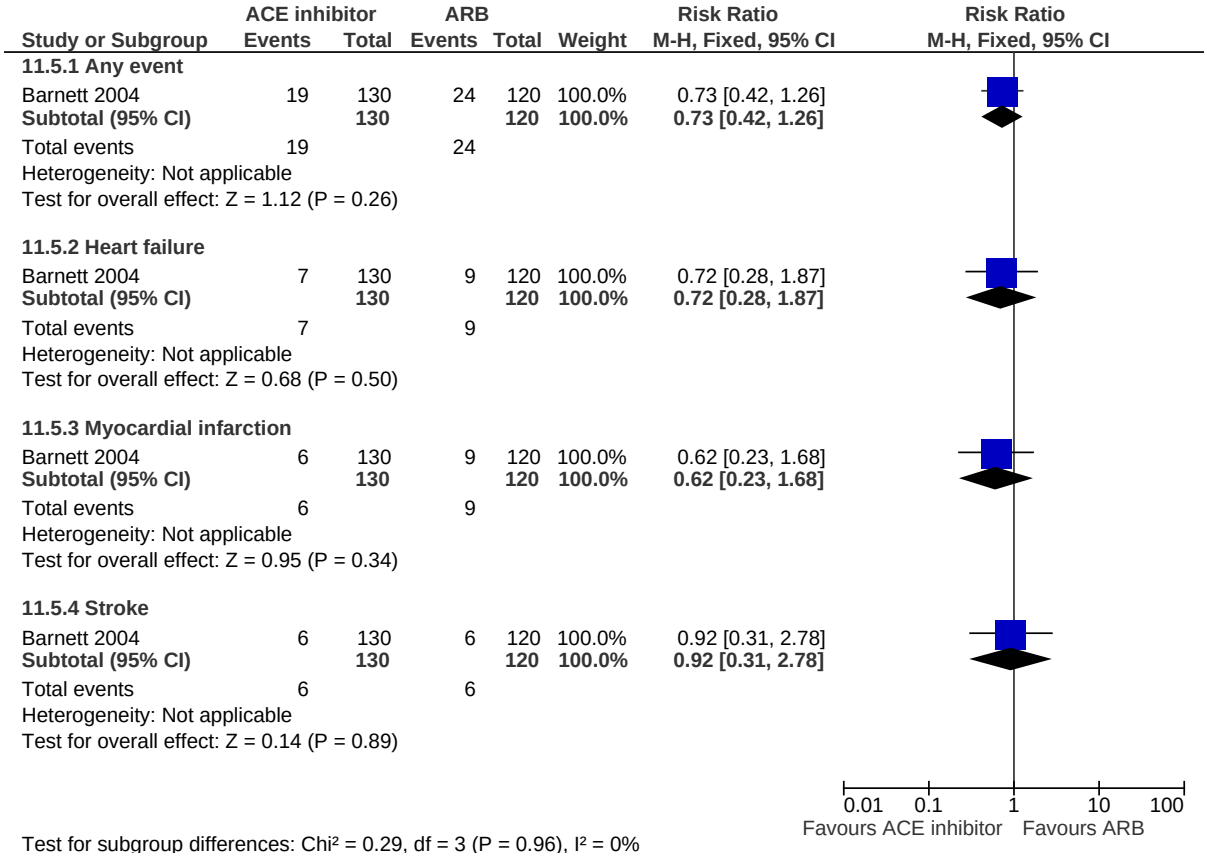
I.9.4.4 Cardiovascular mortality

Figure 172: ACE inhibitor vs.ARB in people with CKD and diabetes



I.9.4.5 Cardiovascular events

Figure 173: ACE inhibitor vs.ARB in people with CKD and diabetes

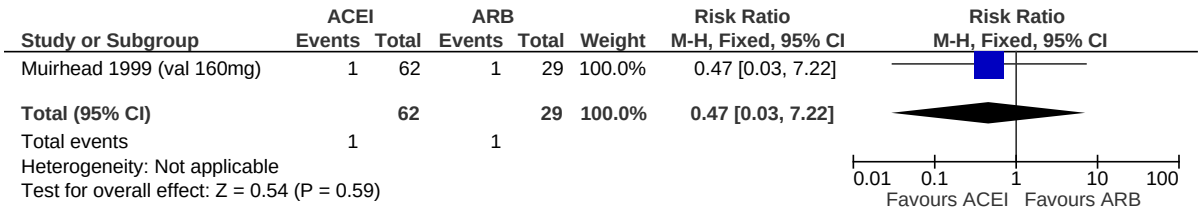


Test for subgroup differences: Chi² = 0.29, df = 3 (P = 0.96), I² = 0%

I.9.4.6 Change in proteinuria

Progression to macroalbuminuria

Figure 174: ACE inhibitor vs.ARB in people with CKD and type II diabetes



Change from baseline

Figure 175: ACE vs.ARB in people with IgA nephropathy (subgroup by dose)

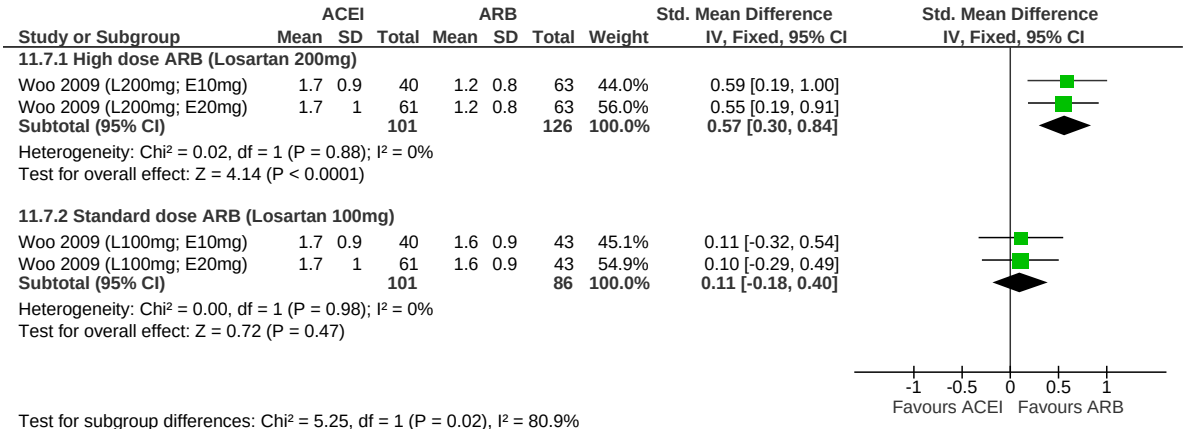


Figure 176: ACE vs.ARB in people with CKD with IgA nephropathy or type II diabetes (pooled doses)

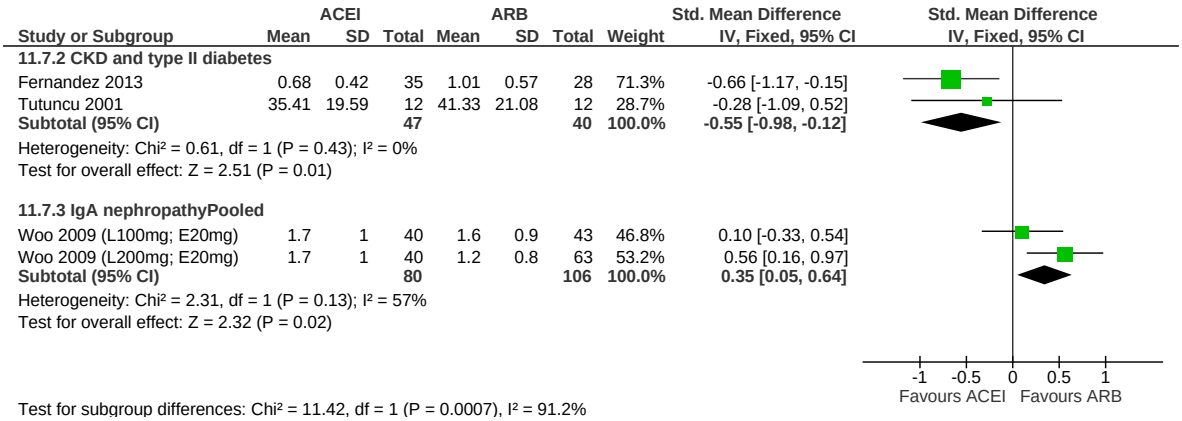
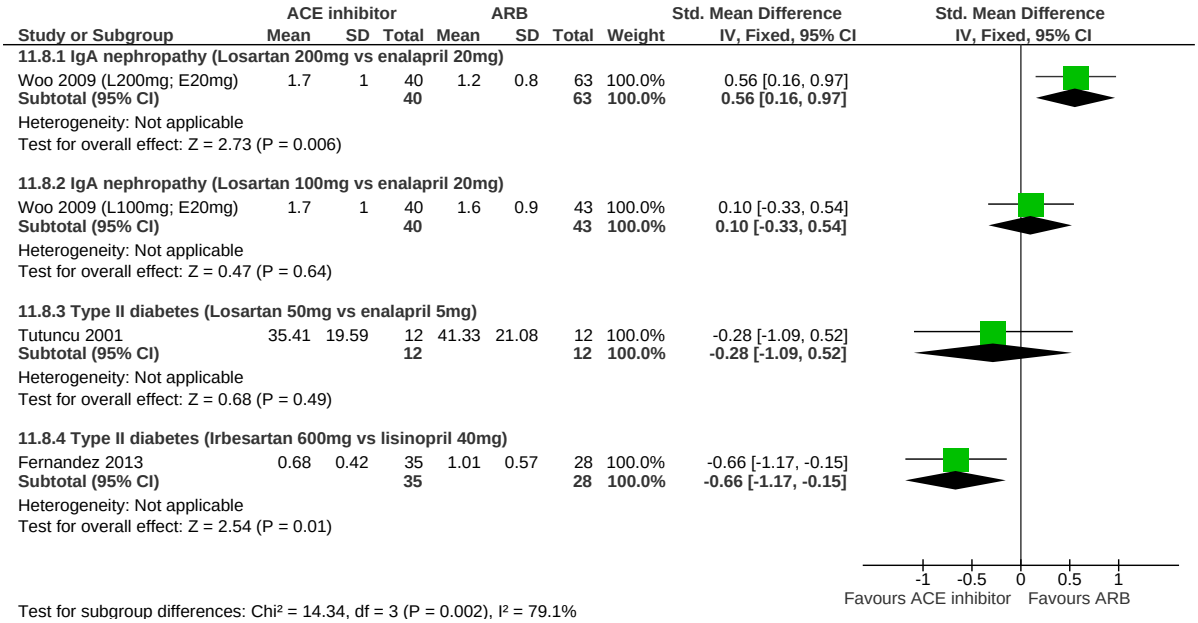
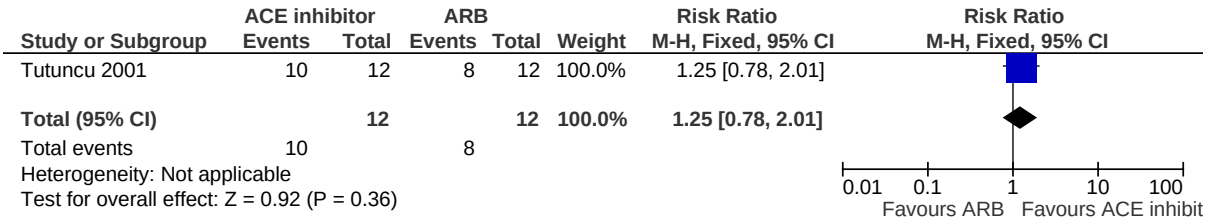


Figure 177: ACE vs.ARB in people with IgA nephropathy or type II diabetes (subgroup by drug)



I.9.4.7 Regression to normoalbuminuria

Figure 178: ACE inhibitor vs.ARB in people with CKD and type II diabetes



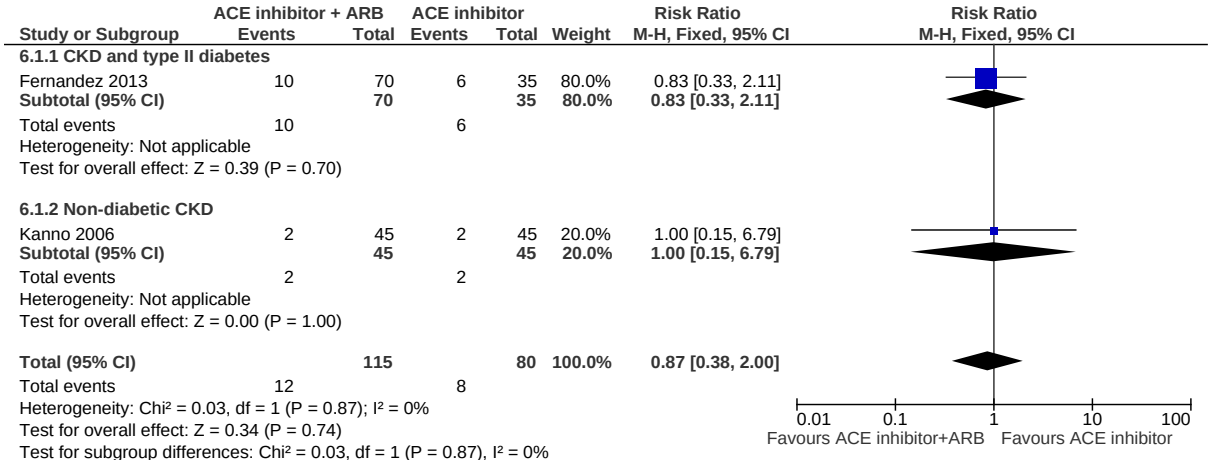
I.9.4.8 Hospitalisation (due to heart failure)

I.9.4.9 Hospitalisation (for non-fatal myocardial infarction, heart failure, peripheral vascular disease or cerebrovascular accident).

I.9.5 ACE inhibitor plus ARB versus ACE inhibitor

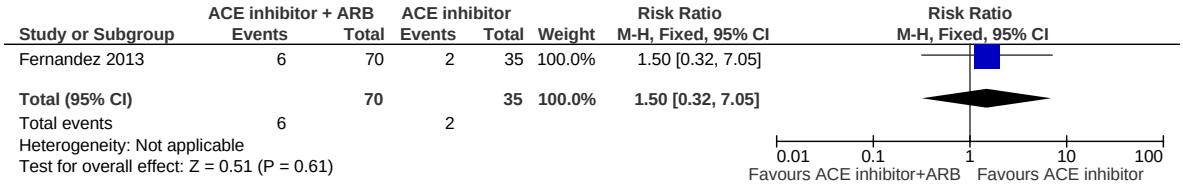
I.9.5.1 Progression of CKD – Occurrence of end stage renal disease

Figure 179: ACE inhibitor plus ARB vs.ACE inhibitor in people with CKD (with and without diabetes)



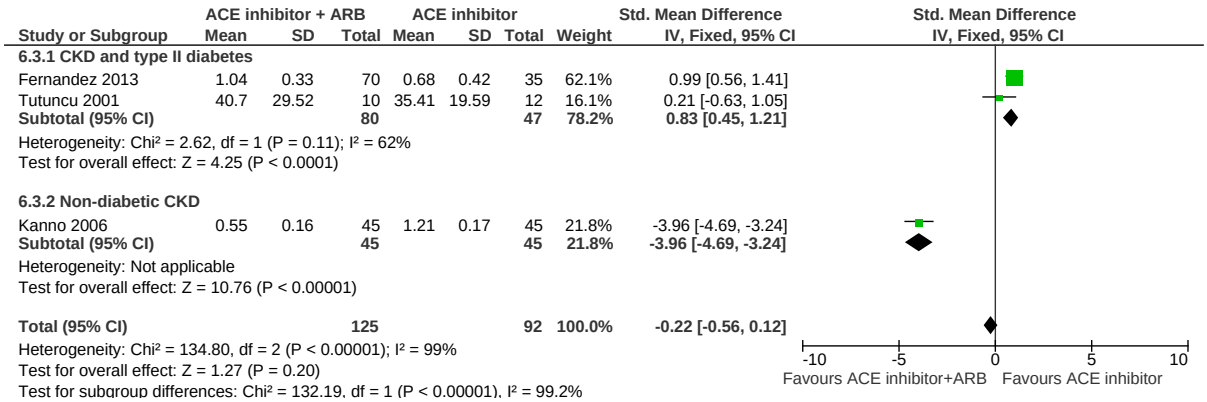
I.9.5.2 All-cause mortality

Figure 180: ACE inhibitor plus ARB vs.ACE inhibitor in people with CKD and type II diabetes



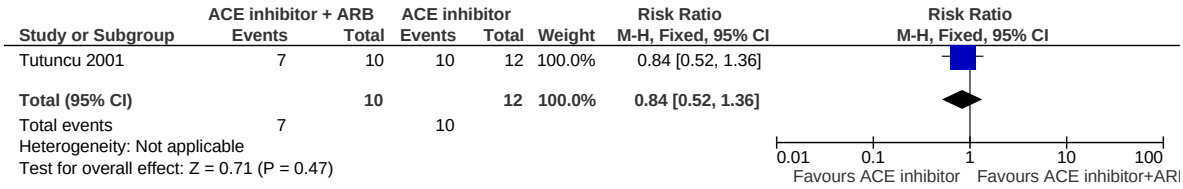
I.9.5.3 Change in proteinuria

Figure 181: ACE inhibitor plus ARB vs.ACE inhibitor in people with or without diabetes– final values in urinary protein loss



I.9.5.4 Regression to normoalbuminuria

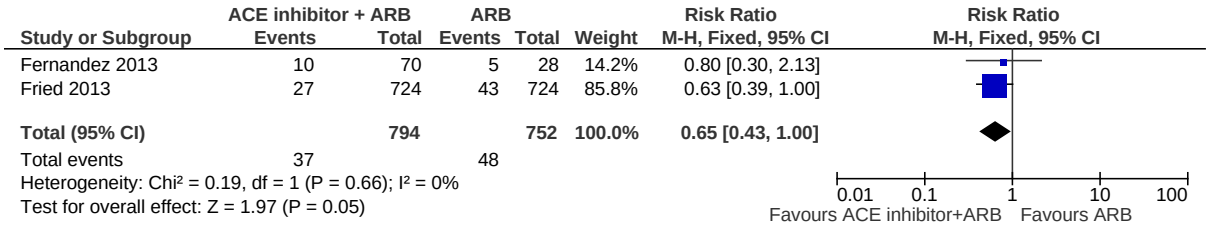
Figure 182: ACE inhibitor plus ARB vs.ACE inhibitor in people with type II diabetes



I.9.6 ACE inhibitor plus ARB versus ARB

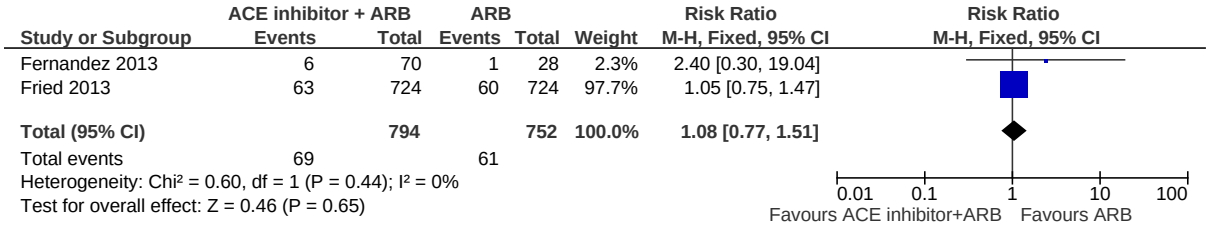
I.9.6.1 Progression of CKD – Occurrence of end stage renal disease

Figure 183: ACE inhibitor plus ARB vs.ARB in people with type II diabetes



I.9.6.2 All-cause mortality

Figure 184: ACE inhibitor plus ARB vs.ARB in people with type II diabetes



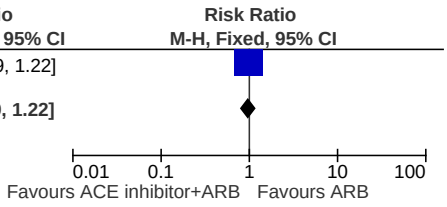
I.9.6.3 Cardiovascular events

Occurrence of myocardial infarction, heart failure or stroke

Figure 185: ACE inhibitor plus ARB vs.ARB in people with type II diabetes

Study or Subgroup	ACE inhibitor + ARB Events	Total	ARB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fried 2013	134	724	136	724	100.0%	0.99 [0.79, 1.22]
Total (95% CI)		**724**		**724**	**100.0%**	**0.99 [0.79, 1.22]**
Total events	134		136			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)

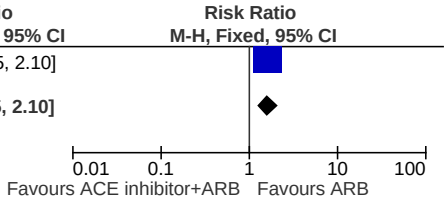


I.9.6.4 Occurrence of AKI

Figure 186: ACE inhibitor plus ARB vs.ARB in people with type II diabetes

Study or Subgroup	ACE inhibitor + ARB Events	Total	ARB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fried 2013	130	724	80	724	100.0%	1.63 [1.25, 2.10]
Total (95% CI)		**724**		**724**	**100.0%**	**1.63 [1.25, 2.10]**
Total events	130		80			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.68 (P = 0.0002)

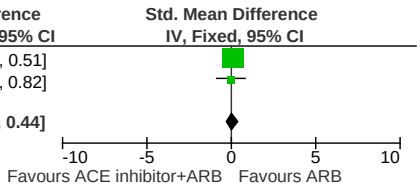


I.9.6.5 Change in proteinuria

Figure 187: ACE inhibitor plus ARB vs.ARB – final values in urinary protein loss in people with type II diabetes

Study or Subgroup	ACE inhibitor + ARB Mean	SD	Total	ARB Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Fernandez 2013	1.04	0.33	70	1.01	0.57	28	78.6%	0.07 [-0.37, 0.51]
Tutuncu 2001	40.7	29.52	10	41.33	21.08	12	21.4%	-0.02 [-0.86, 0.82]
Total (95% CI)			**80**			**40**	**100.0%**	**0.05 [-0.34, 0.44]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)

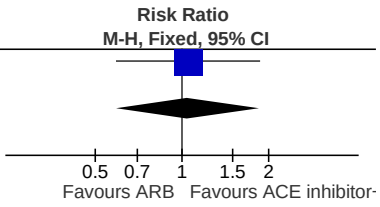


I.9.6.6 Regression to normoalbuminuria

Figure 188: ACE inhibitor plus ARB vs.ARB in people with type II diabetes

Study or Subgroup	ACE inhibitor + ARB Events	Total	ARB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tutuncu 2001	7	10	8	12	100.0%	1.05 [0.59, 1.86]
Total (95% CI)		**10**		**12**	**100.0%**	**1.05 [0.59, 1.86]**
Total events	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)

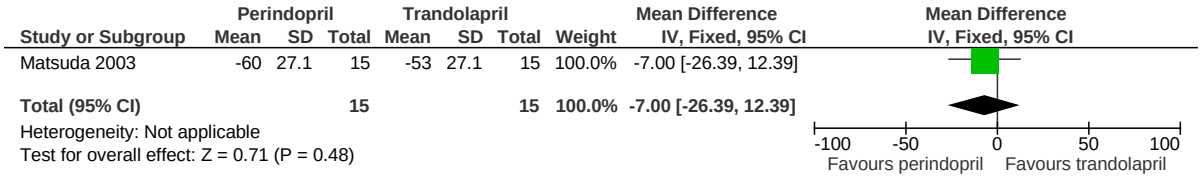


I.9.7 ACE inhibitor versus ACE inhibitor

I.9.7.1 Change in proteinuria

Percentage change

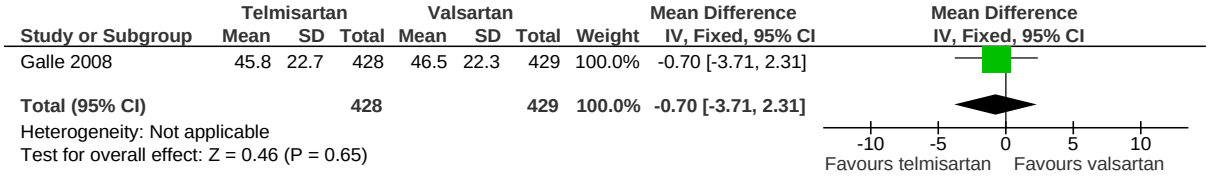
Figure 189: Perindopril (6.6mg/day) vs.trandolapril (1.8mg/day) in people with non-diabetic CKD (final achieved doses)



I.9.8 ARB versus ARB: Telmisartan versus valsartan

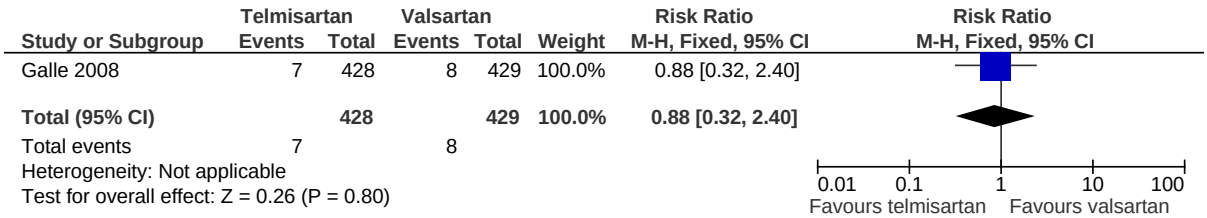
I.9.8.1 Progression of CKD – measured by change in eGFR

Figure 190: Telmisartan (80mg) vs.valsartan (160mg) in people with CKD and type II diabetes



I.9.8.2 Progression of CKD – Occurrence of end stage renal disease

Figure 191: Telmisartan (80mg) vs.valsartan (160mg) in people with CKD and type II diabetes

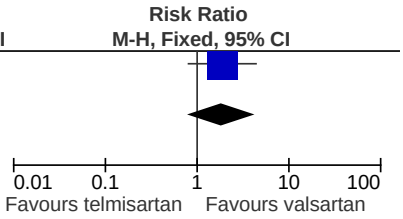


I.9.8.3 All-cause mortality

Figure 192: Telmisartan (80mg) vs.valsartan (160mg) in people with CKD and type II diabetes

Study or Subgroup	Telmisartan Events	Total	Valsartan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galle 2008	15	428	8	429	100.0%	1.88 [0.81, 4.39]
Total (95% CI)		**428**		**429**	**100.0%**	**1.88 [0.81, 4.39]**
Total events	15		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)

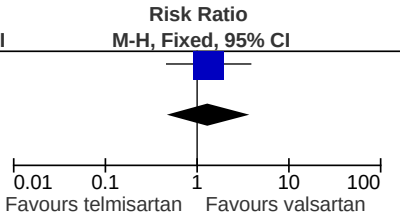


I.9.8.4 Cardiovascular mortality

Figure 193: Telmisartan (80mg) vs.valsartan (160mg) in people with CKD and type II diabetes

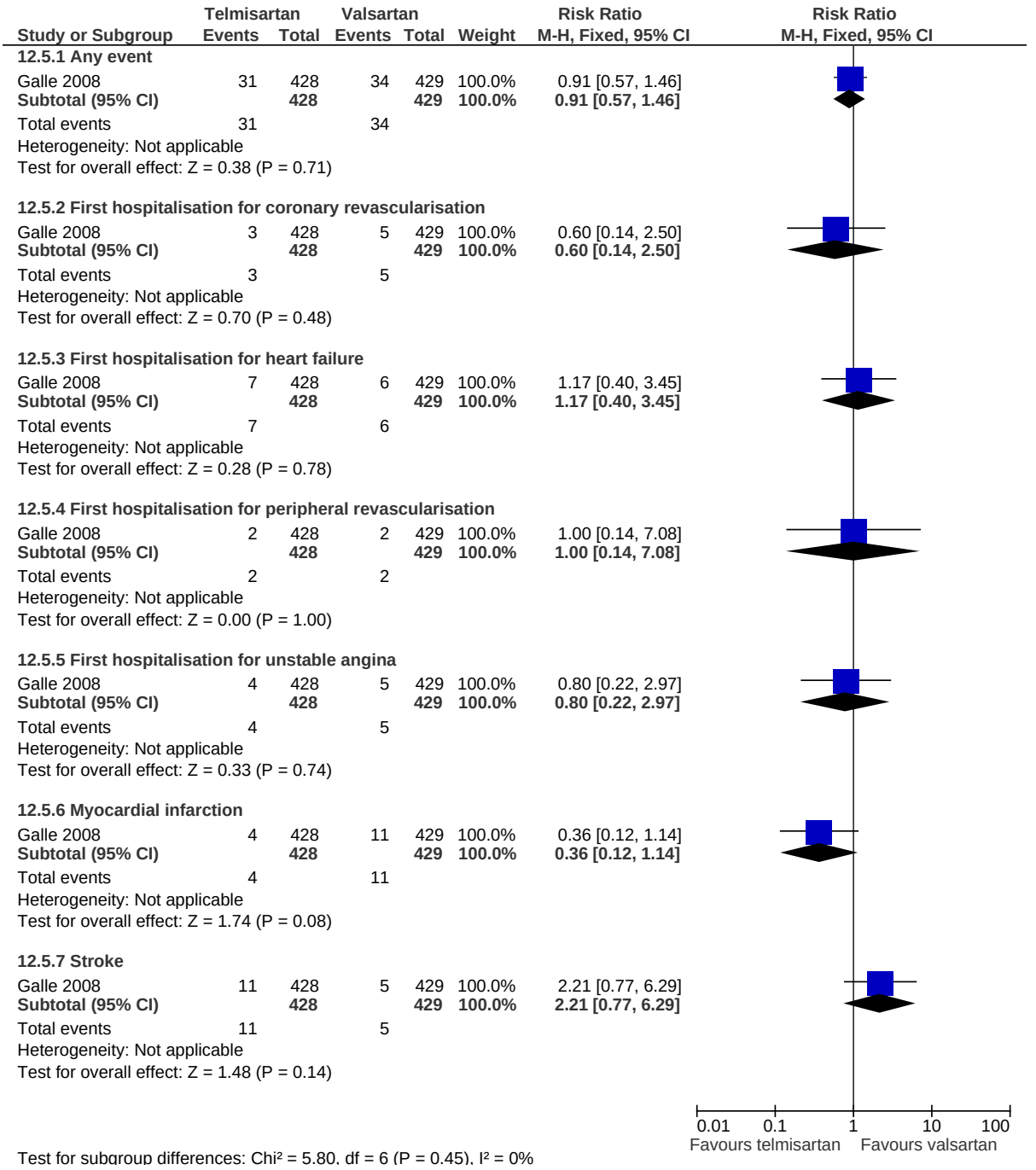
Study or Subgroup	Telmisartan Events	Total	Valsartan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galle 2008	8	428	6	429	100.0%	1.34 [0.47, 3.82]
Total (95% CI)		**428**		**429**	**100.0%**	**1.34 [0.47, 3.82]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



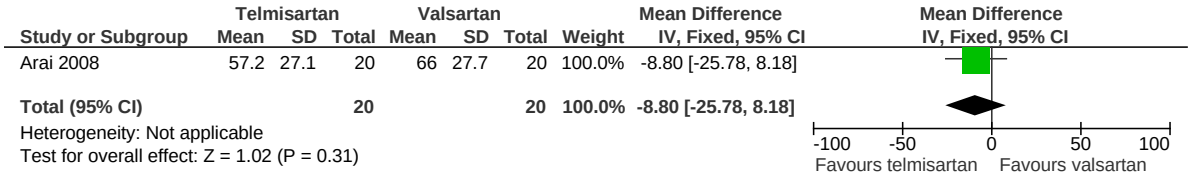
I.9.8.5 Cardiovascular events

Figure 194: Telmisartan (80mg) vs.valsartan (160mg) in people with CKD and type II diabetes



I.9.8.6 Change in proteinuria

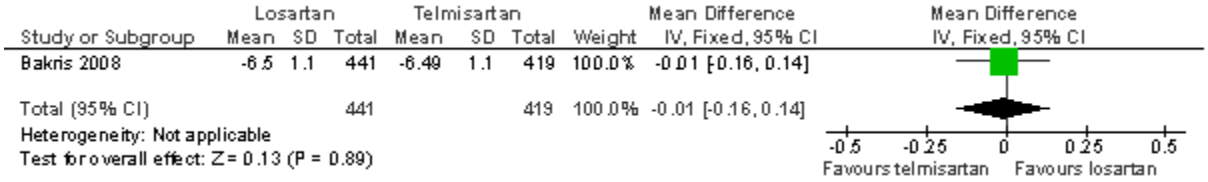
Figure 195: Change in final albumin excretion rate, mg/day (Final doses: telmisartan 48mg/day, valsartan 116 mg/day) in people with CKD and type II diabetes



I.9.9 ARB versus ARB: Losartan versus telmisartan

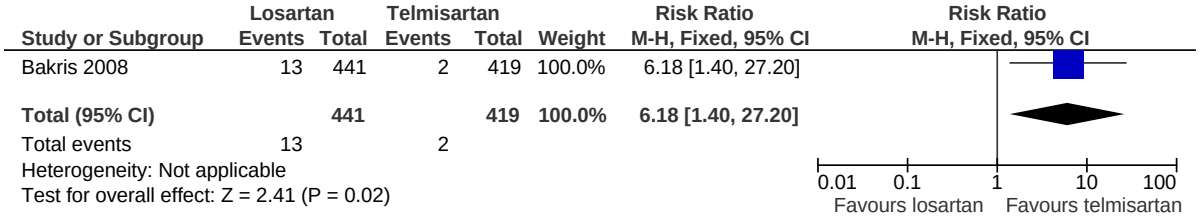
I.9.9.1 Progression of CKD – measured by change in eGFR

Figure 196: Losartan (100mg) vs.telmisartan (80mg) in people with CKD and type II diabetes



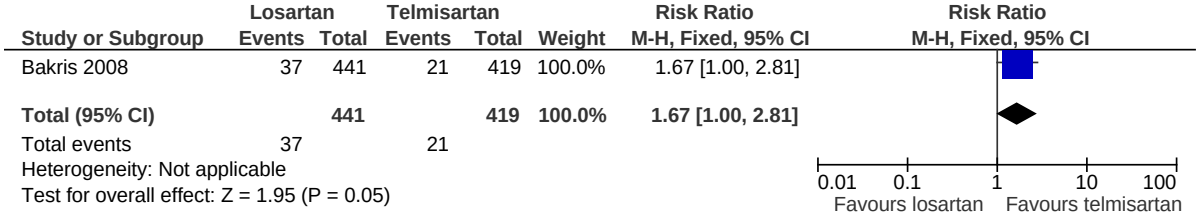
I.9.9.2 All-cause mortality

Figure 197: Losartan (100mg) vs.telmisartan (80mg) in people with CKD and type II diabetes



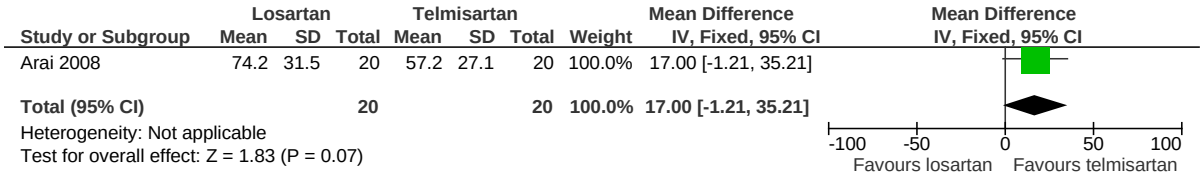
I.9.9.3 Cardiovascular morbidity or mortality

Figure 198: Losartan (100mg) vs.telmisartan (80mg) in people with CKD and type II diabetes



I.9.9.4 Change in proteinuria

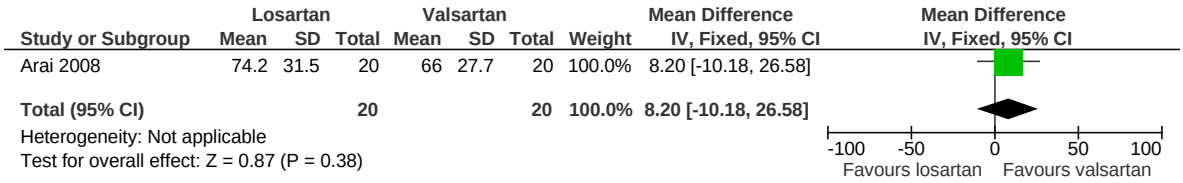
Figure 199: Change in urinary albumin excretion, mg/day (Final doses: losartan 71.3mg/day, telmisartan 48mg/day) in people with CKD and type II diabetes



I.9.10 ARB versus ARB: Losartan versus valsartan

I.9.10.1 Change in proteinuria

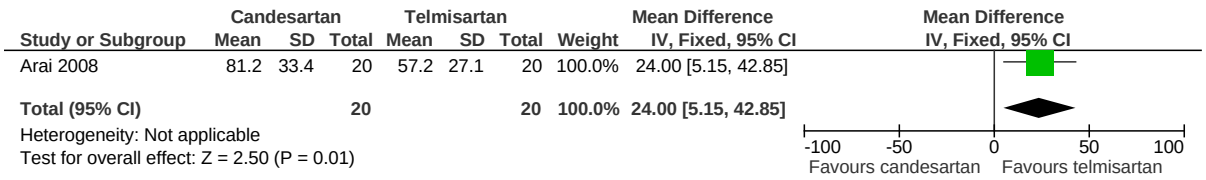
Figure 200: Change in final albumin excretion rate, mg/day (Final doses: losartan 71.3mg/day, valsartan 116mg/day) in people with CKD and type II diabetes



I.9.11 ARB versus ARB: Candesartan versus telmisartan

I.9.11.1 Change in proteinuria

Figure 201: Change in final albumin excretion rate, mg/day (Final doses: candesartan 10.2mg/day, telmisartan 48mg/day) in people with CKD and type II diabetes



I.9.12 ARB versus ARB: Candesartan versus losartan

I.9.12.1 Change in proteinuria

Figure 202: Change in final albumin excretion rate, mg/day (Final doses: candesartan 10.2mg/day, losartan 71.3mg/day) in people with type II diabetes

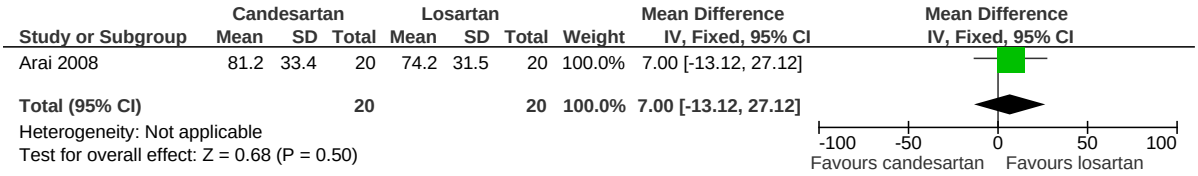
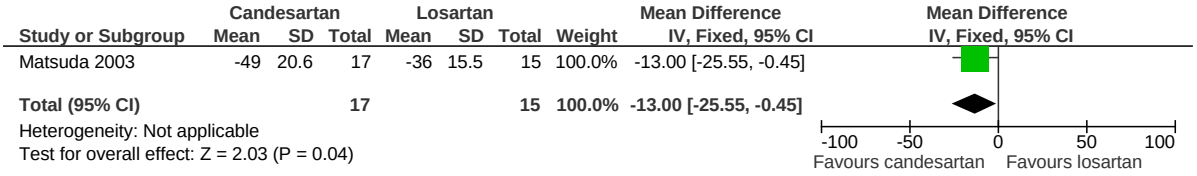
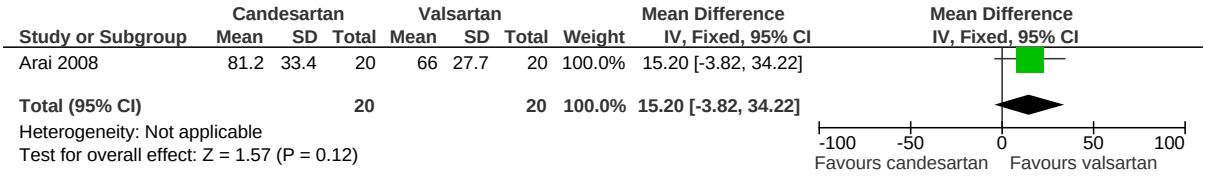


Figure 203: Percentage change in urinary protein excretion rate (Final doses: candesartan 7.8mg/day, losartan 81mg/day) in people with non-diabetic CKD



Candesartan vs.valsartan in people with CKD and type II diabetes

Figure 204: Change in final albumin excretion rate, mg/day (Final doses: candesartan 10.2mg/day, valsartan 116mg/day)

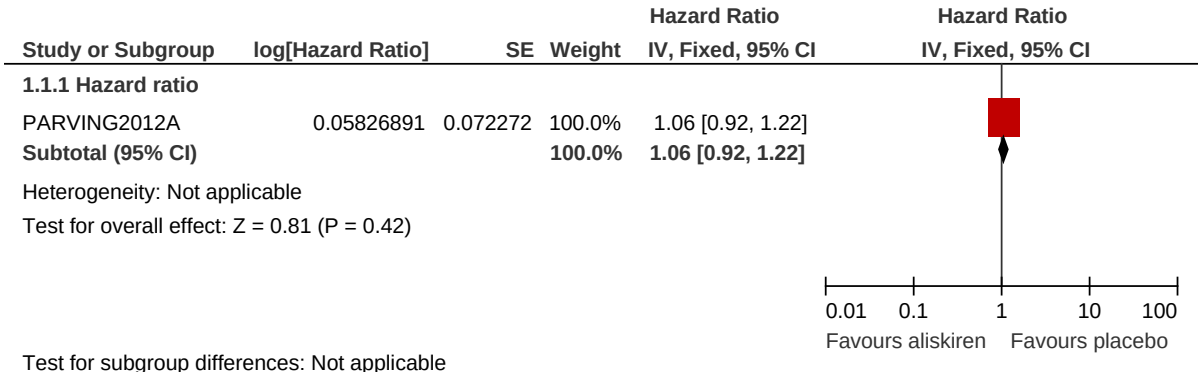


I.9.13 Direct renin inhibitor versus placebo

I.9.14 Aliskiren (300mg) versus placebo on a background of ACE inhibitor or ARB in people with type II diabetes and micro / marcoalbuminuria Progression of CKD – measured by change in eGFR

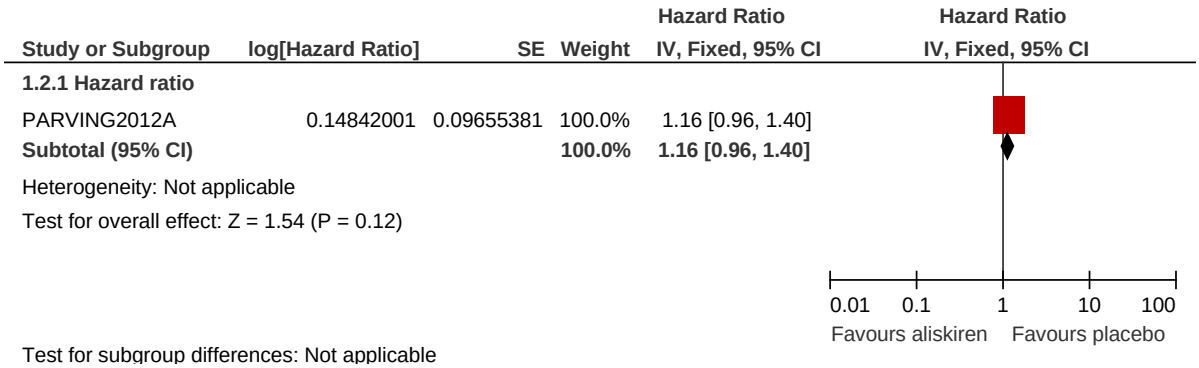
I.9.14.1 All-cause mortality

Figure 205: All-cause mortality (aliskiren 300mg) on a background of ACE inhibitor / ARB



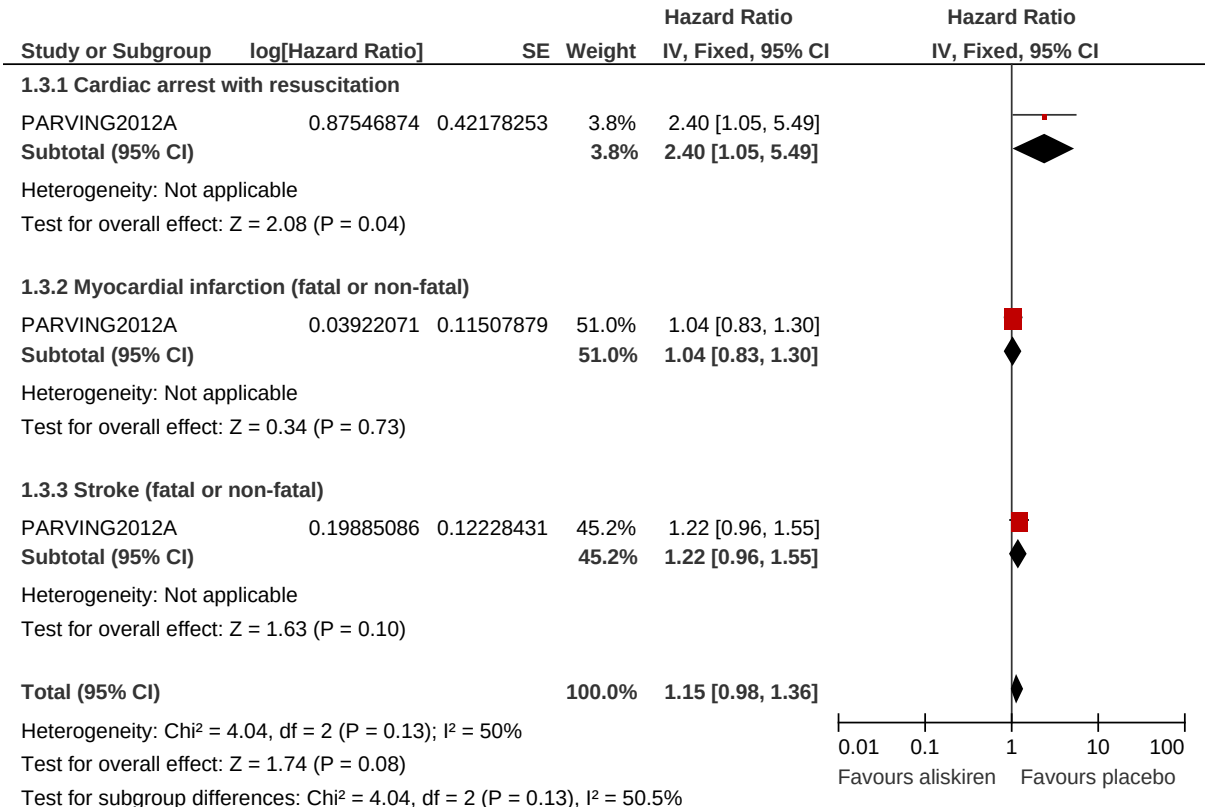
I.9.14.2 Cardiovascular mortality

Figure 206: Cardiovascular mortality (aliskiren 300mg) on a background of ACE inhibitor / ARB



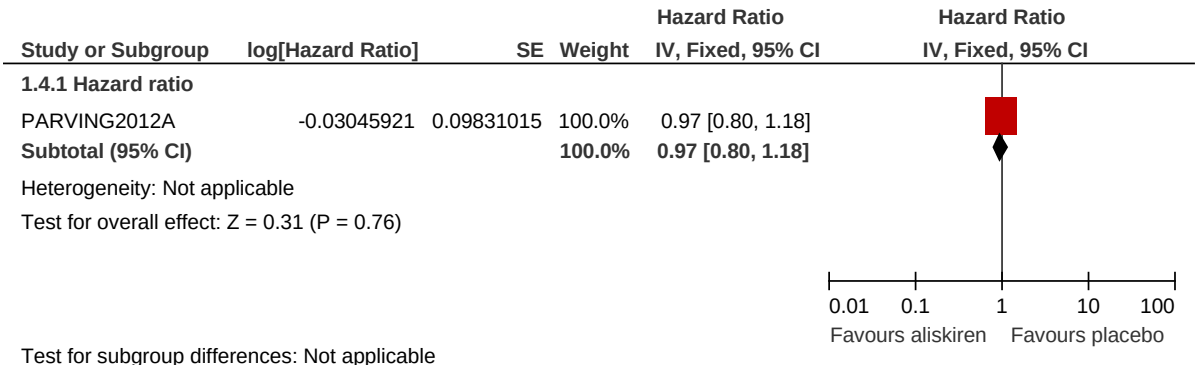
I.9.14.3 Cardiovascular events

Figure 207: Cardiovascular events (aliskiren 300mg) on a background of ACE inhibitor / ARB



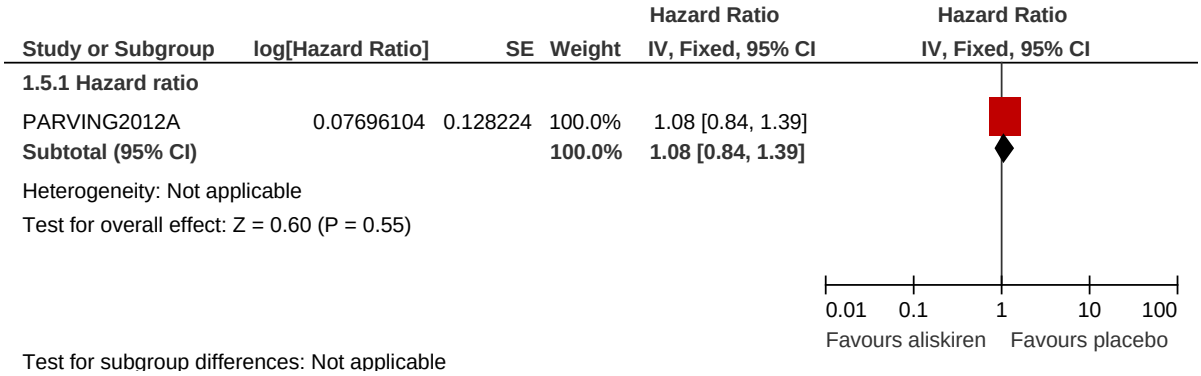
I.9.14.4 Hospitalisation (due to heart failure)

Figure 208: Unplanned hospitalisation due to heart failure (aliskiren 300mg) on a background of ACE inhibitor / ARB



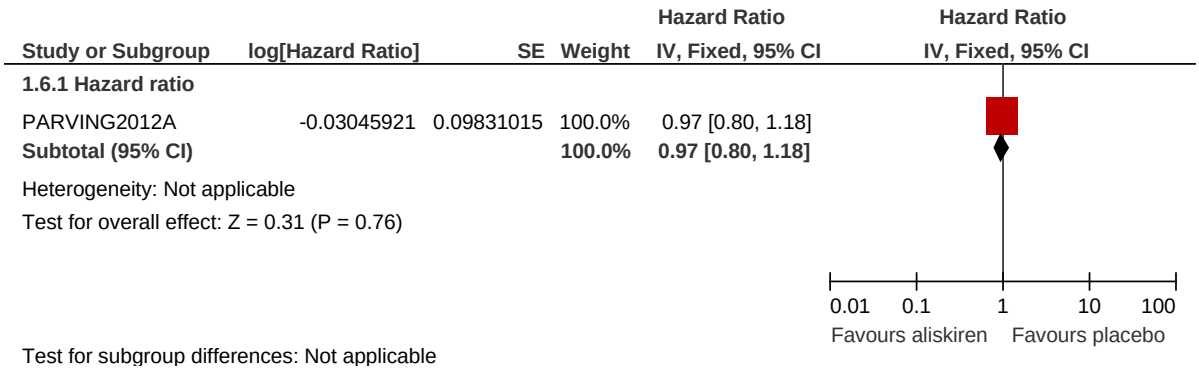
I.9.14.5 Progression of CKD: ESRD, death attributable to kidney failure or loss of kidney function (need for RRT with no dialysis or transplantation available or initiated)

Figure 209: ESRD, death attributable to kidney failure or loss of kidney function (aliskiren 300mg) on a background of ACE inhibitor / ARB



I.9.14.6 Progression of CKD: Doubling of baseline serum creatinine

Figure 210: Doubling of baseline serum creatinine (aliskiren 300mg) on a background of ACE inhibitor / ARB

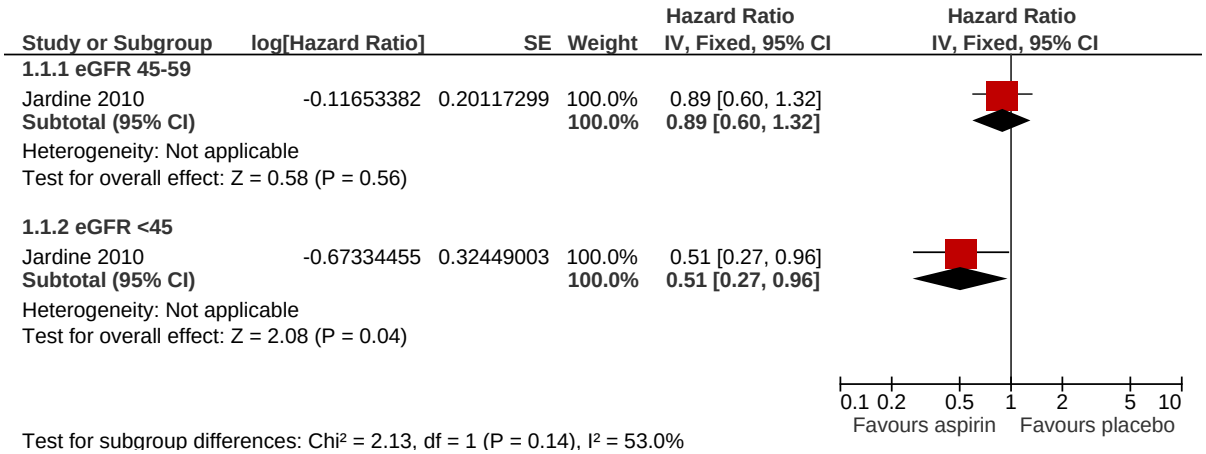


I.10 Oral anticoagulants and antiplatelets

I.10.1 Aspirin (75mg/day) versus placebo

I.10.1.1 All-cause mortality

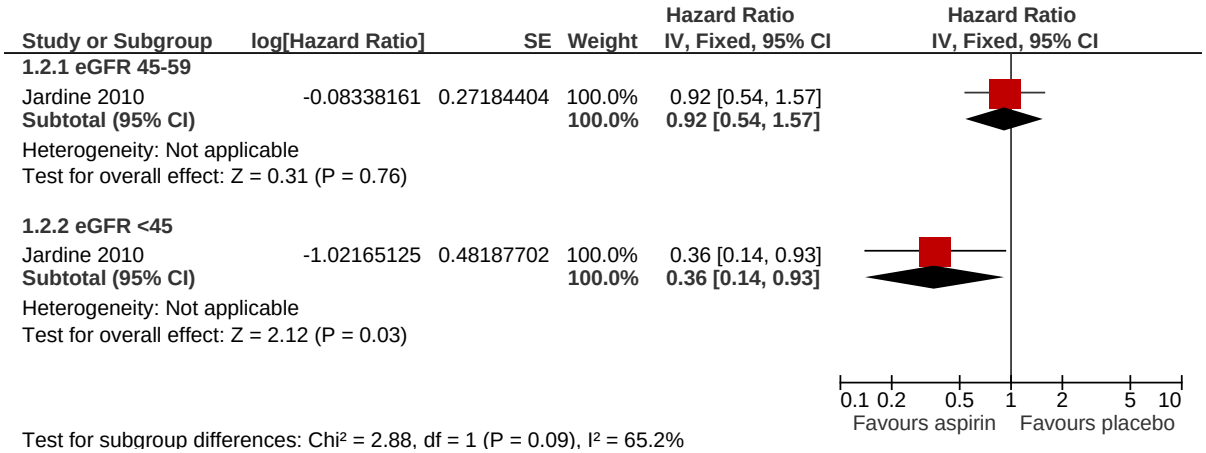
Figure 211: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



Test for subgroup differences: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.0%

I.10.1.2 Cardiovascular mortality

Figure 212: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years

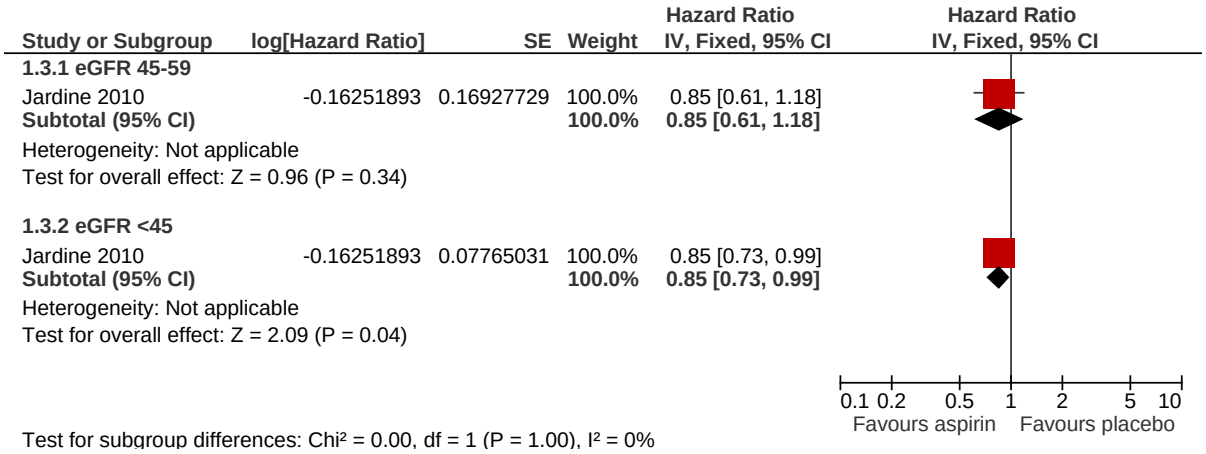


Test for subgroup differences: Chi² = 2.88, df = 1 (P = 0.09), I² = 65.2%

I.10.1.3 Cardiovascular events

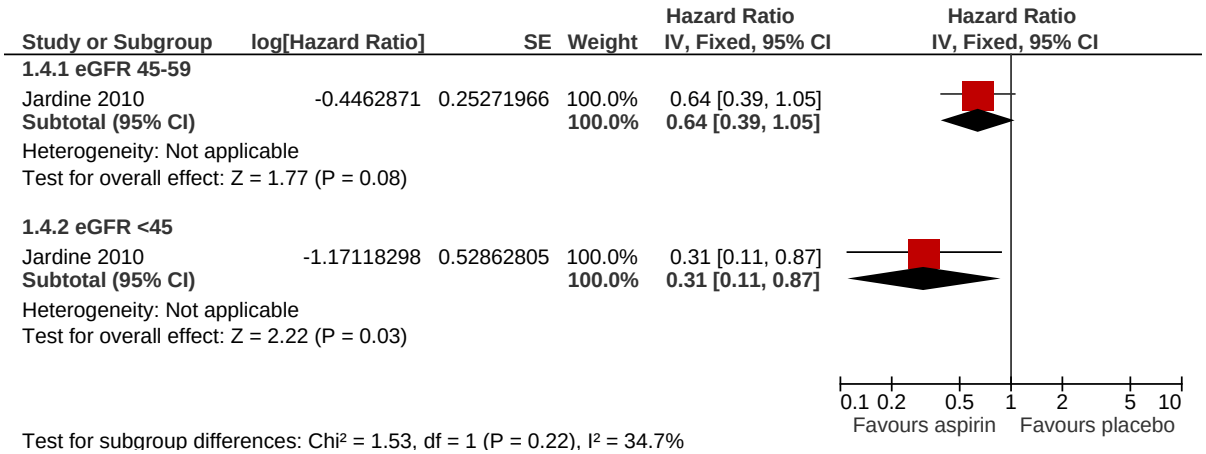
Major cardiovascular event

Figure 213: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



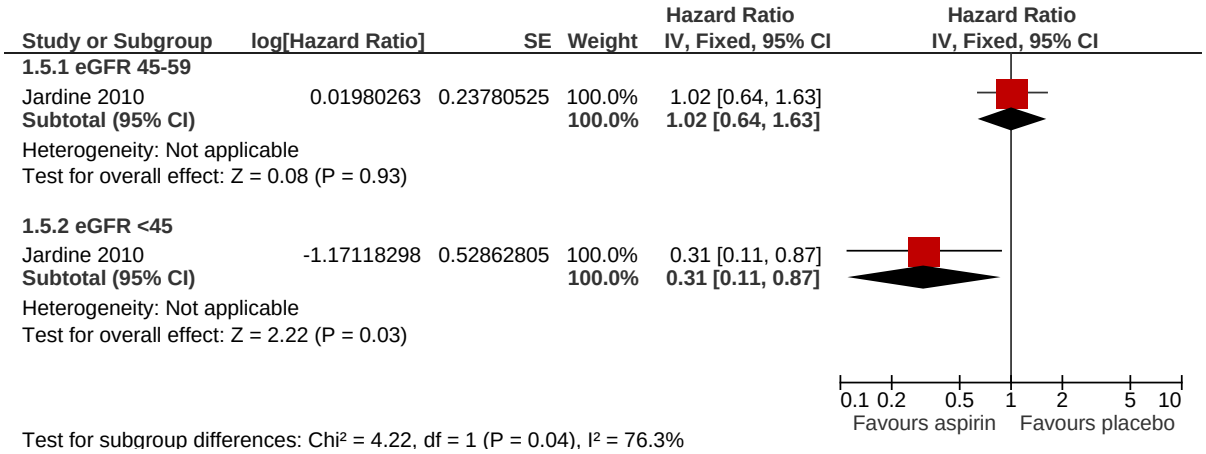
Myocardial infarction

Figure 214: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



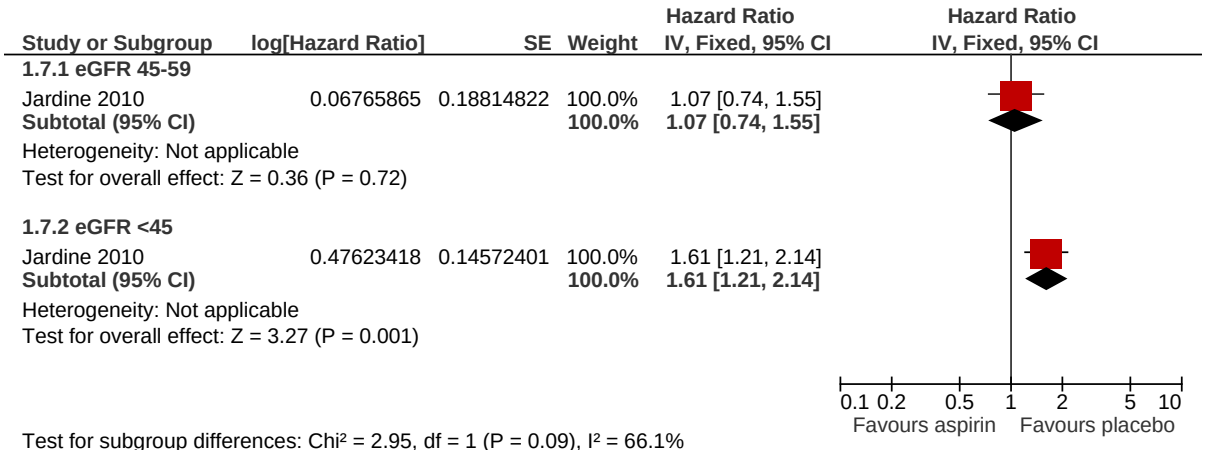
Stroke

Figure 215: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



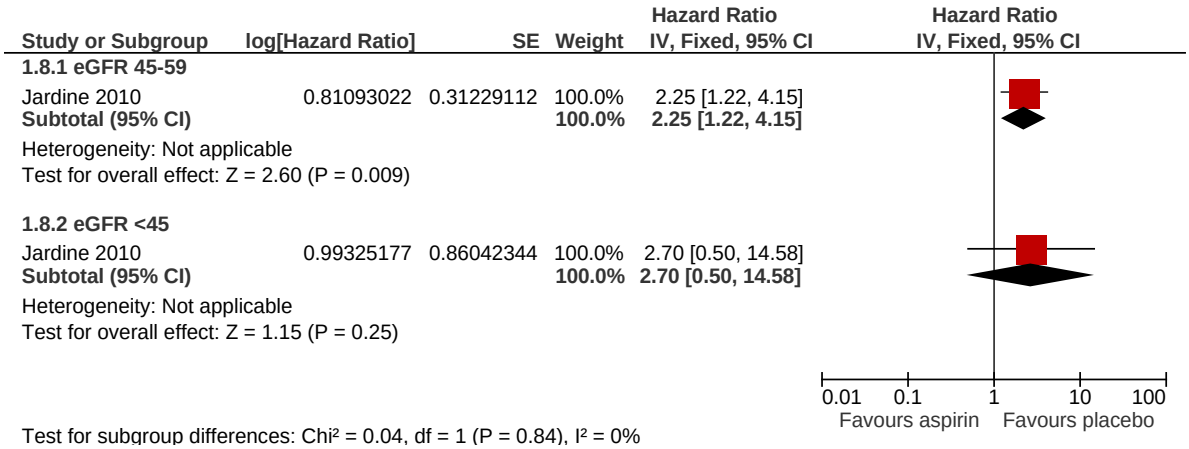
I.10.1.4 Major bleeding (fatal, life-threatening, disabling or requiring hospital admission)

Figure 216: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



I.10.1.5 Minor bleeding

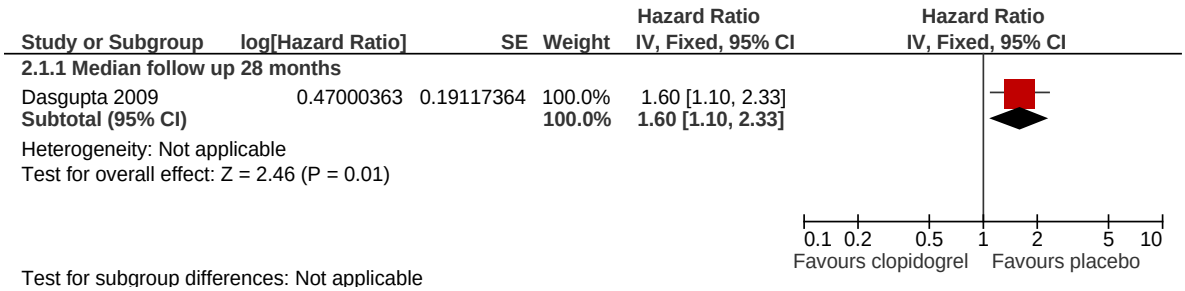
Figure 217: Aspirin versus placebo in people with hypertension and eGFR <60ml/min/1.73m^2, mean follow-up 3.8 years



I.10.2 Clopidogrel (75mg/day) versus placebo

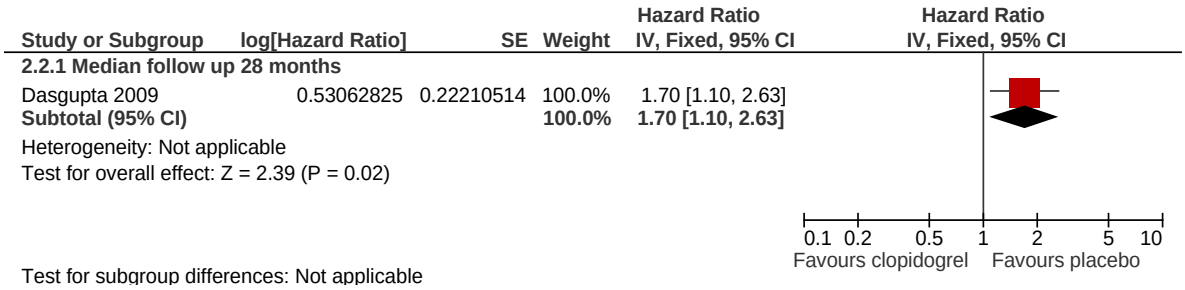
I.10.2.1 All-cause mortality

Figure 218: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



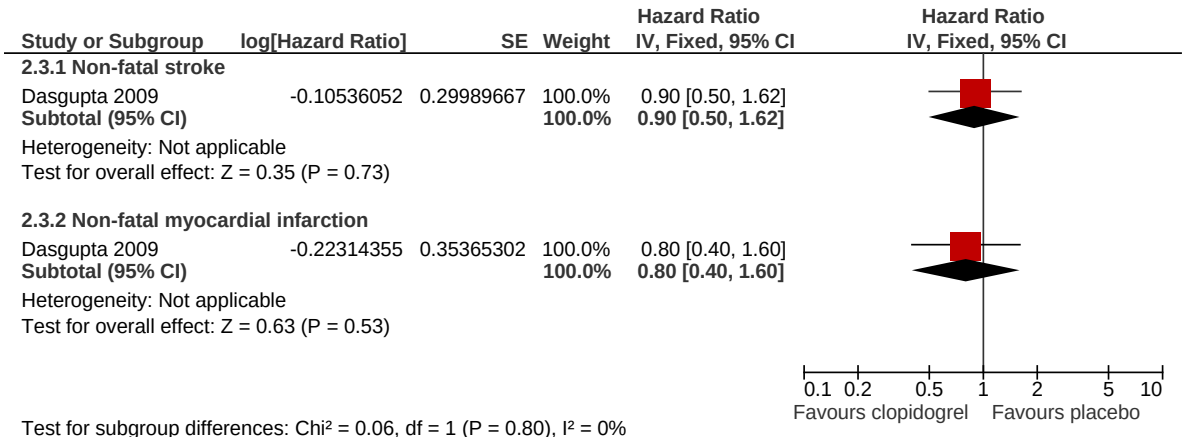
I.10.2.2 Cardiovascular mortality

Figure 219: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



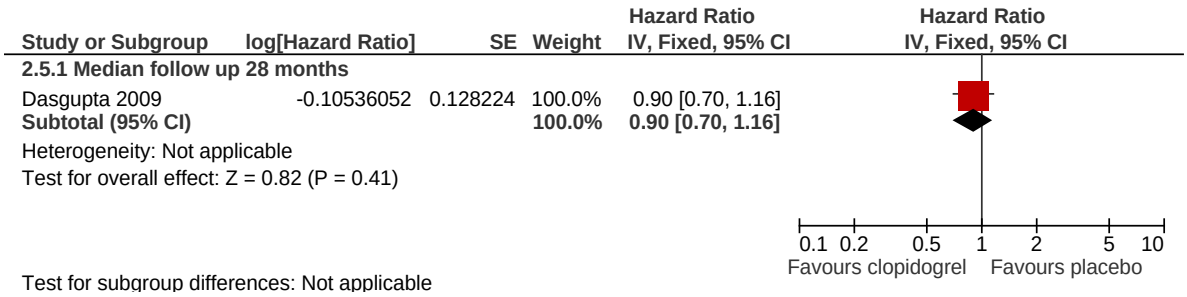
I.10.2.3 Cardiovascular events

Figure 220: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



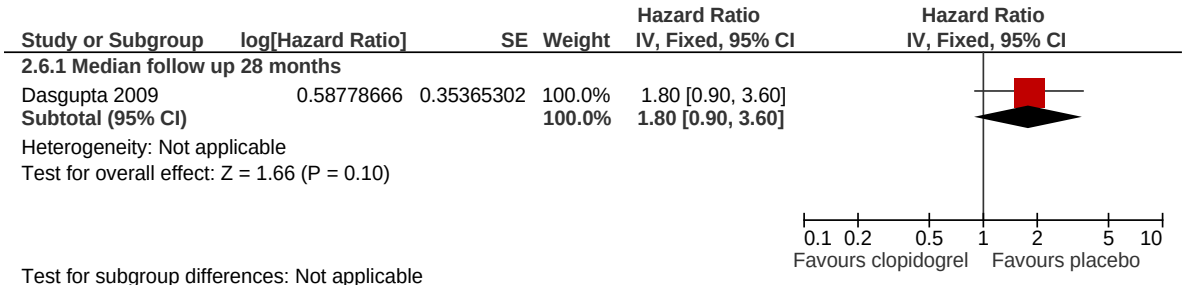
I.10.2.4 Hospitalisation

Figure 221: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



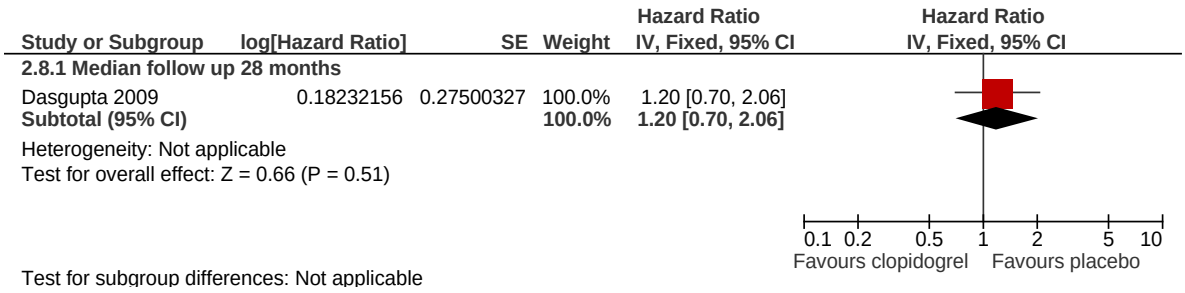
I.10.2.5 Major bleeding (GUSTO severe bleeding)

Figure 222: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



I.10.2.6 Minor bleeding (GUSTO moderate bleeding)

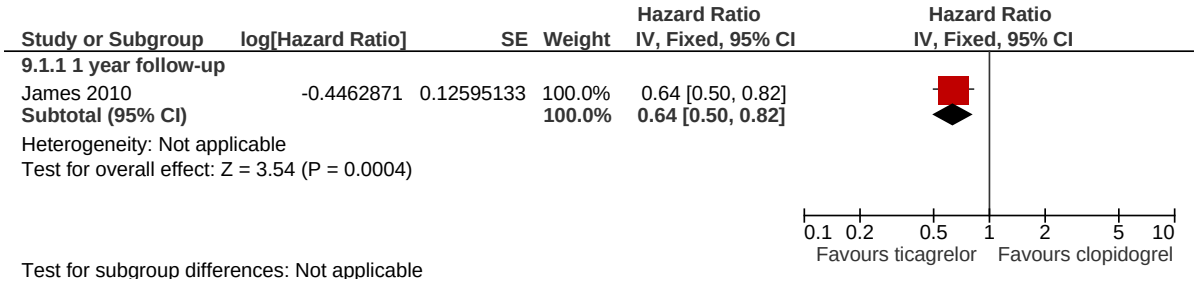
Figure 223: Clopidogrel versus placebo in people with CVD or multiple risk factors for CVD (median follow up 28 months) – subgroup analysis of people with diabetic nephropathy



I.10.3 Ticagrelor (90mg twice daily) versus clopidogrel (75mg daily)

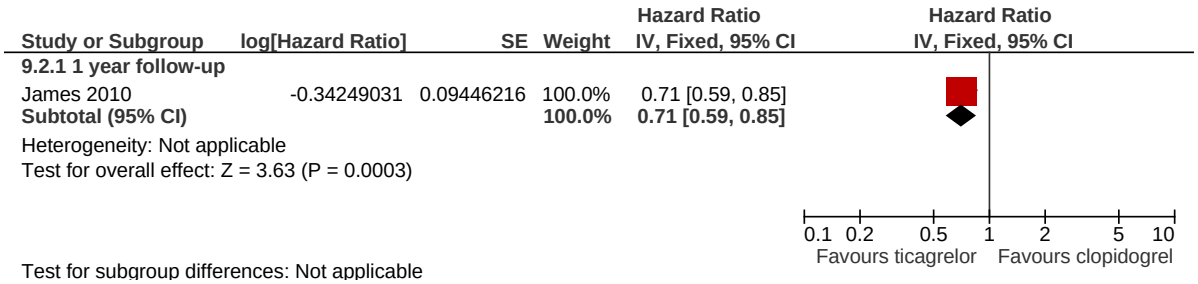
I.10.3.1 All-cause mortality

Figure 224: Ticagrelor versus clopidogrel in people with ST-segment elevation or non ST-segment elevation acute coronary syndrome (1 year follow-up) eGFR<60ml/min/1.73m^2(MDRD)



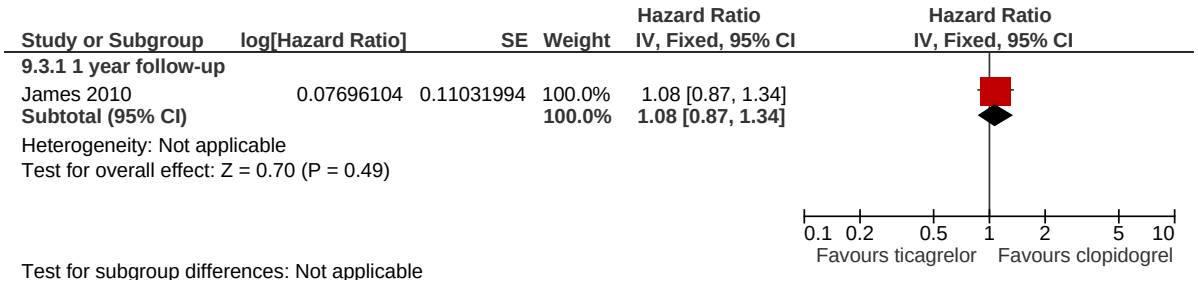
I.10.3.2 Cardiovascular mortality, myocardial infarction or stroke

Figure 225: Ticagrelor versus clopidogrel in people with ST-segment elevation or non ST-segment elevation acute coronary syndrome (1 year follow-up) eGFR<60ml/min/1.73m^2(MDRD)



I.10.3.3 Major bleeding (PLATO defined)

Figure 226: Ticagrelor versus clopidogrel in people with ST-segment elevation or non ST-segment elevation acute coronary syndrome (1 year follow-up) eGFR<60ml/min/1.73m^2(MDRD)



I.10.4 Apixaban versus placebo

I.10.4.1 All-cause mortality (or symptomatic recurrent VTE)

Figure 227: Apixaban 2.5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment

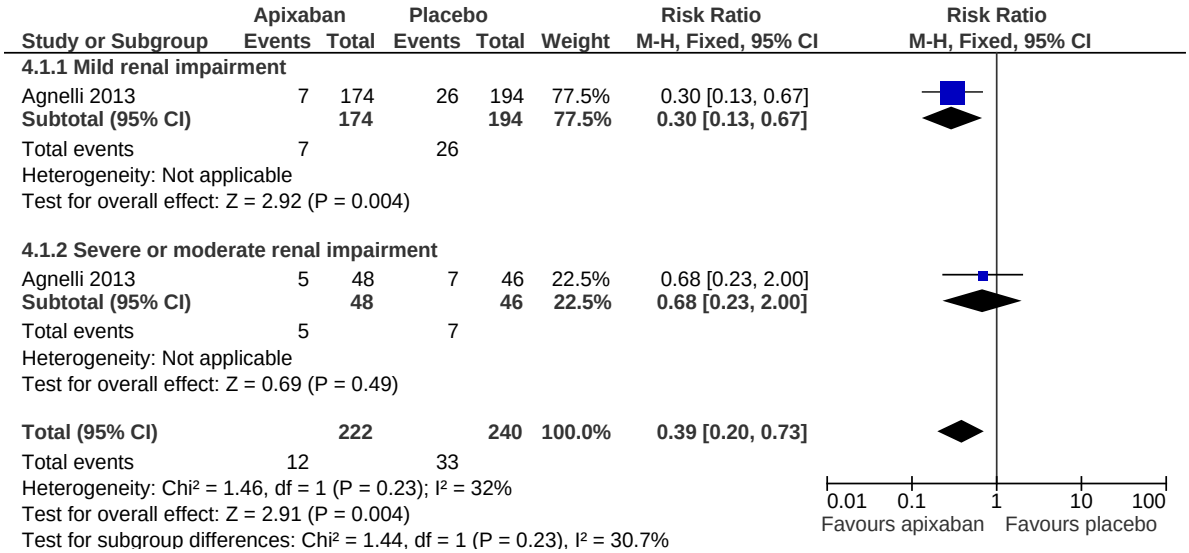
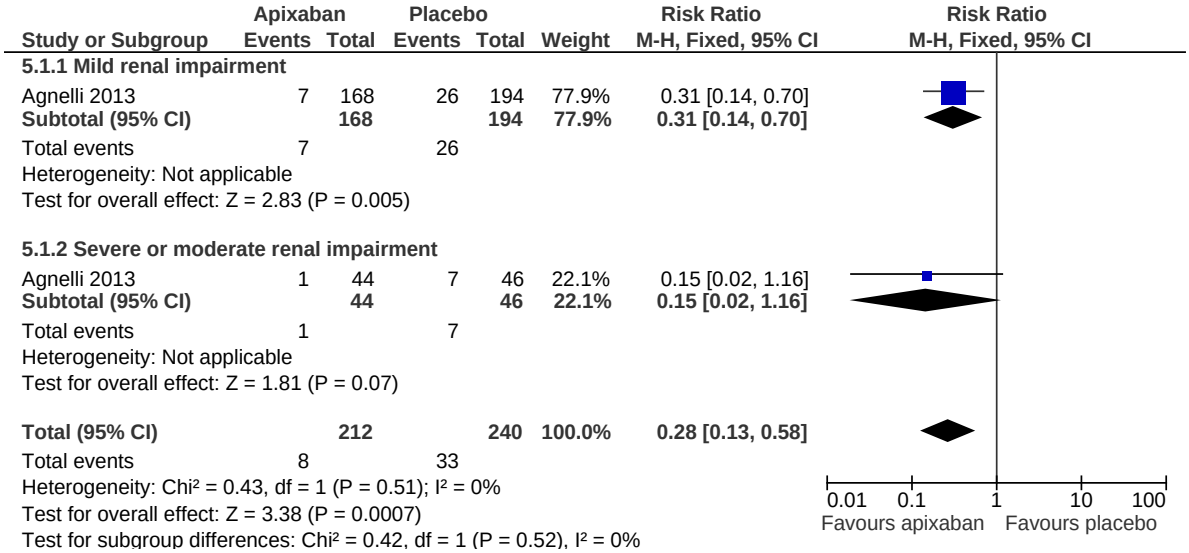
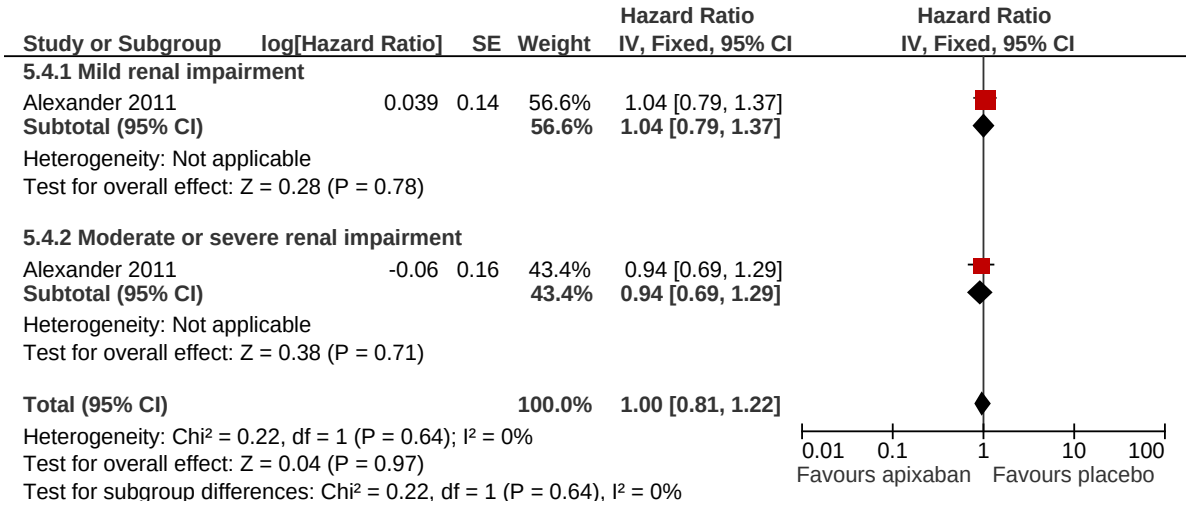


Figure 228: Apixaban 5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment



I.10.4.2 Cardiovascular mortality, MI, ischaemic stroke

Figure 229: Apixaban 5mg versus placebo in people with recent acute coronary syndrome and at least two additional risk factors for recurrent ischaemic events



I.10.4.3 Cardiovascular events (VTE or death due to VTE)

Figure 230: Apixaban 2.5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment

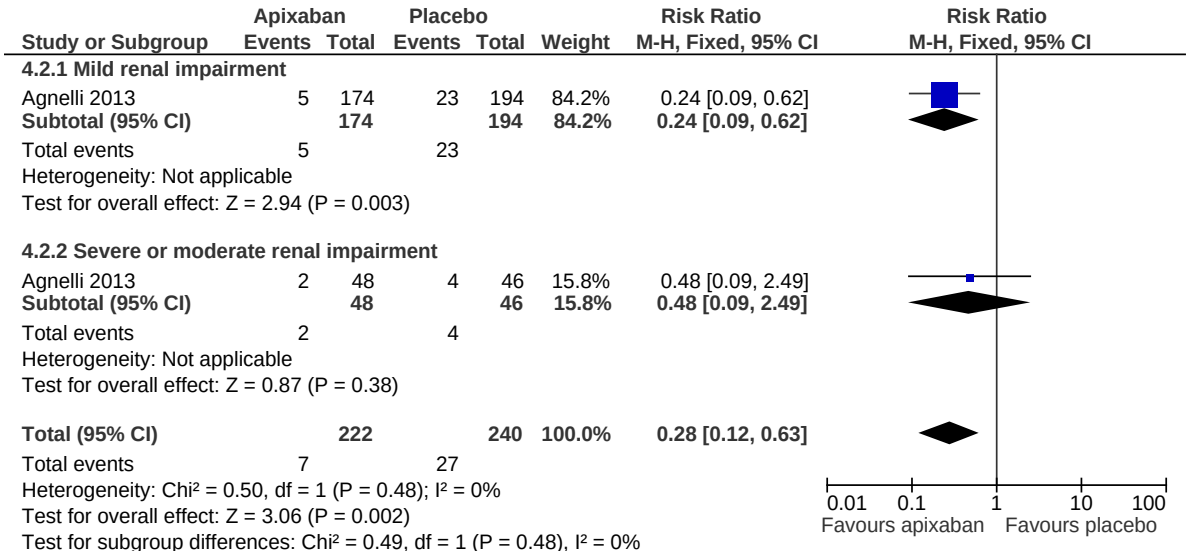
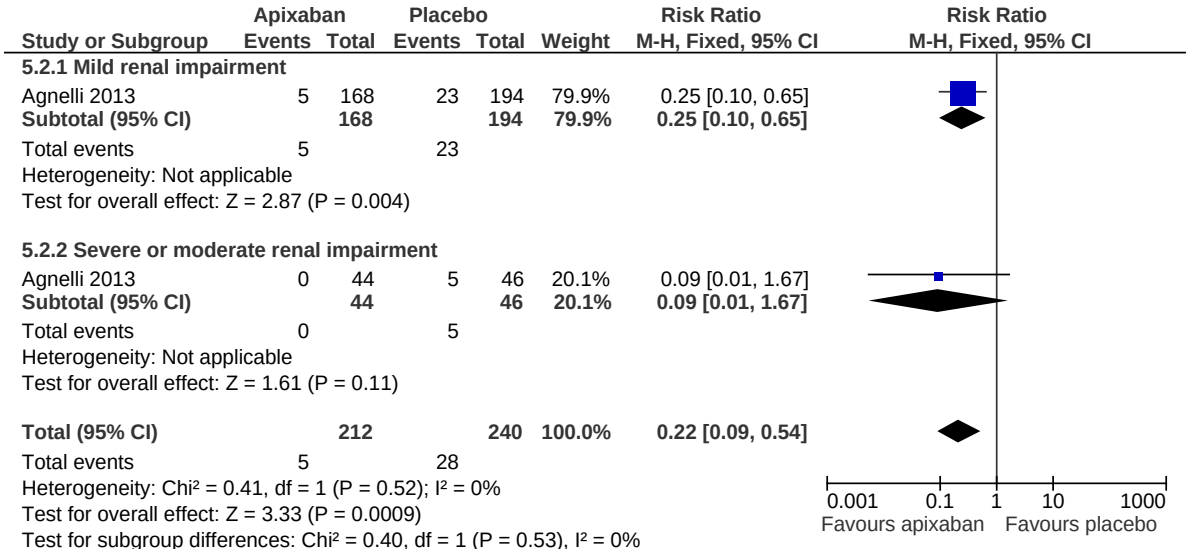


Figure 231: Apixaban 5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment



I.10.4.4 Major bleeding or clinically relevant non-major bleeding

Figure 232: Apixaban 2.5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment

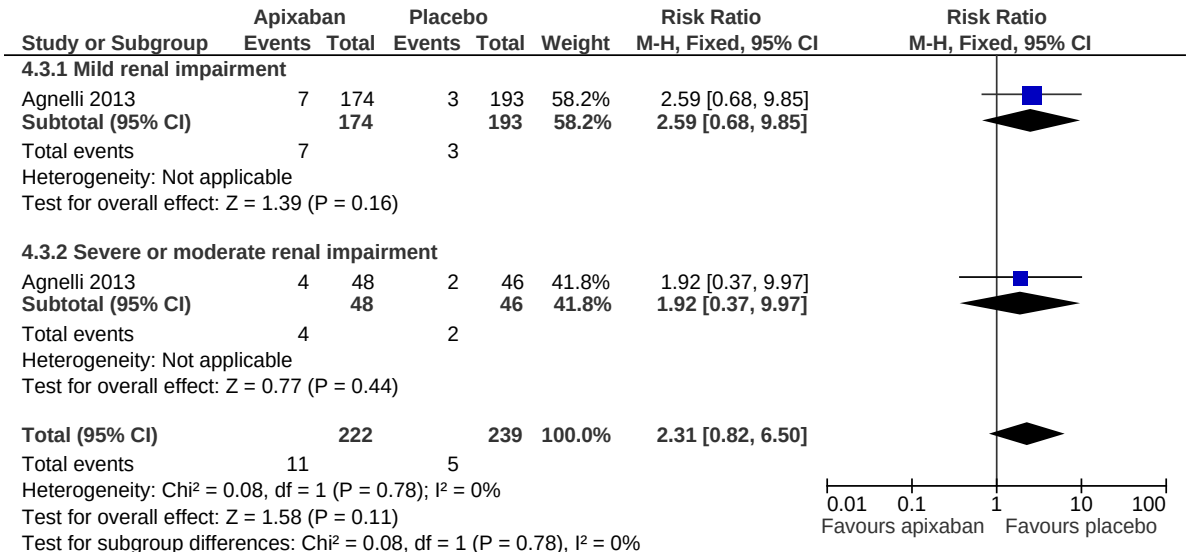
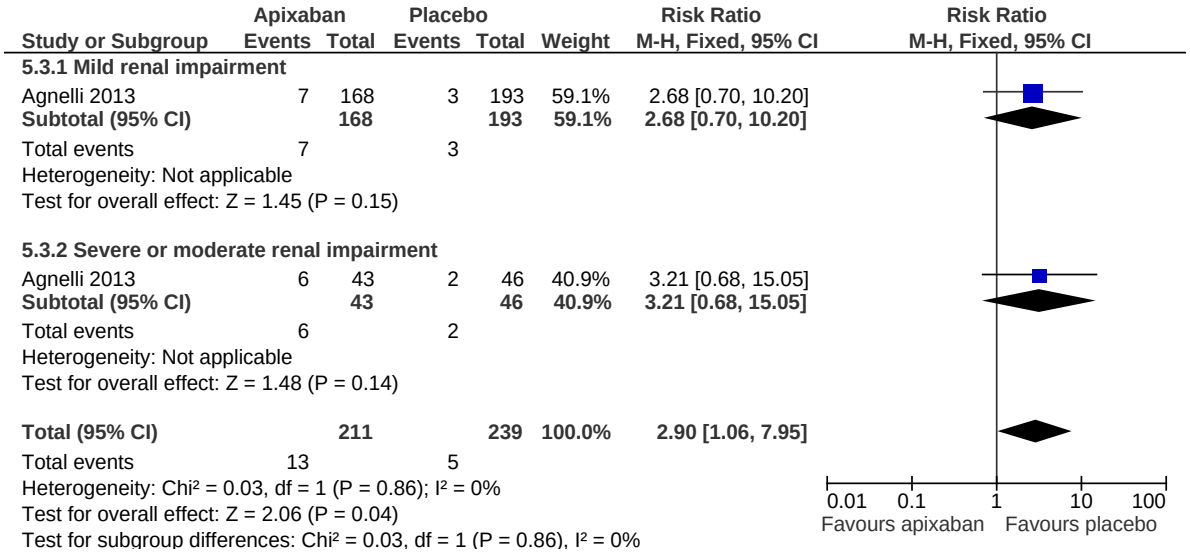
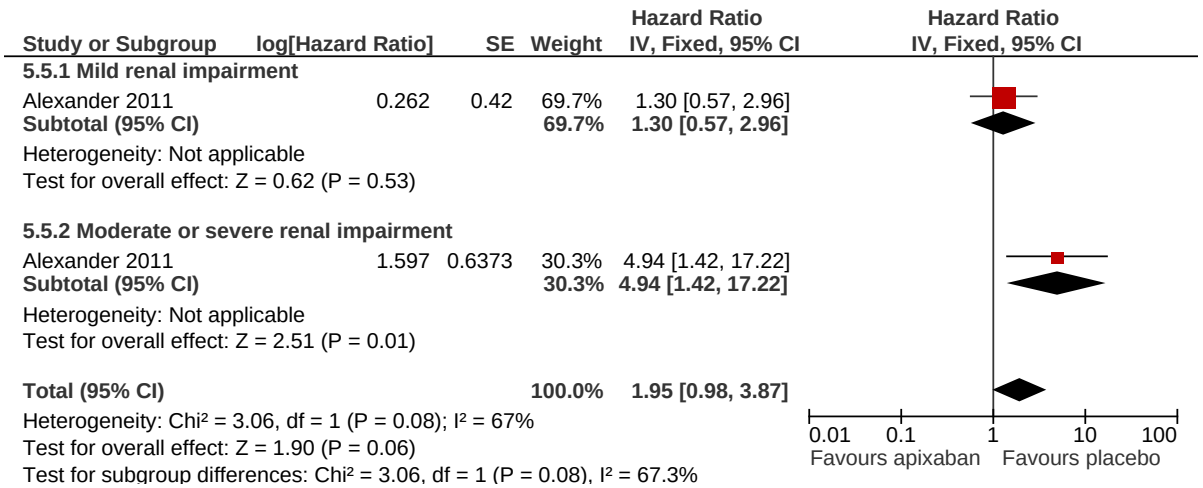


Figure 233: Apixaban 5mg versus placebo in people with symptomatic deep vein thrombosis or pulmonary embolism and renal impairment



I.10.4.5 TIMI major bleeding

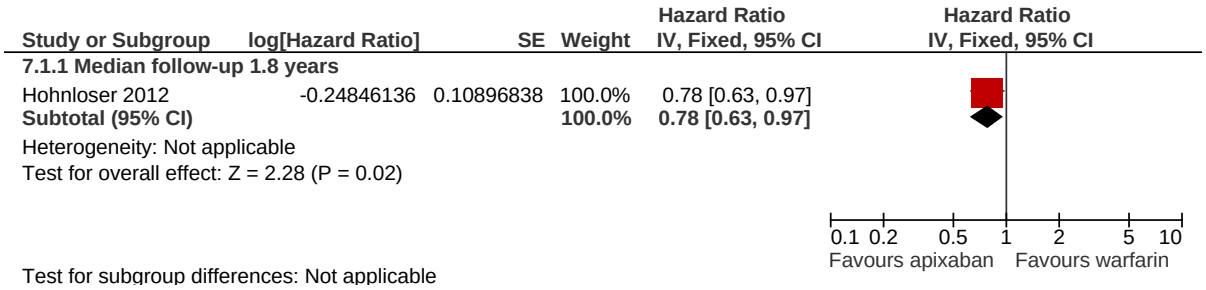
Figure 234: Apixaban 5mg versus placebo in people with recent acute coronary syndrome and at least two additional risk factors for recurrent ischaemic events



I.10.5 Apixaban 2.5 or 5mg twice daily versus warfarin

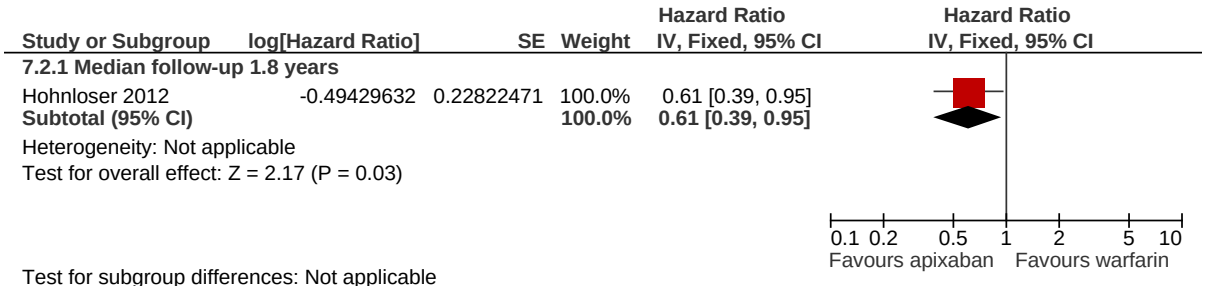
I.10.5.1 All-cause mortality

Figure 235: Apixaban versus warfarin in people with atrial fibrillation and eGFR ≤50ml/min/1.73m^2, median follow-up 1.8 years



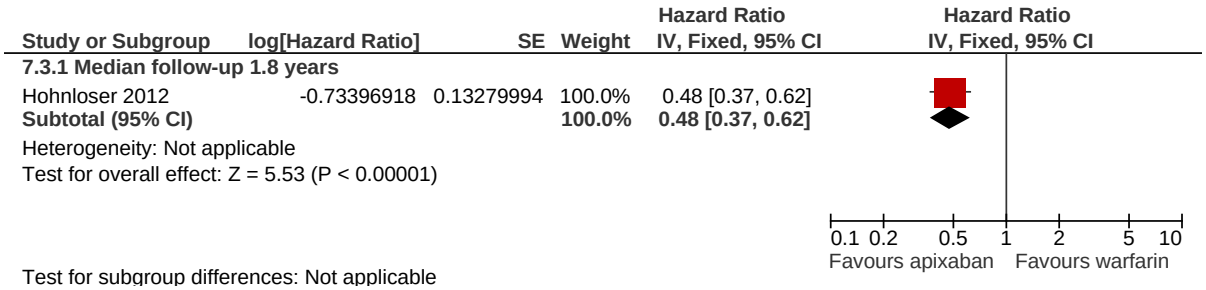
I.10.5.2 Cardiovascular events (stroke and systemic embolism)

Figure 236: Apixaban versus warfarin in people with atrial fibrillation and eGFR ≤50ml/min/1.73m^2, median follow-up 1.8 years



I.10.5.3 Major bleeding

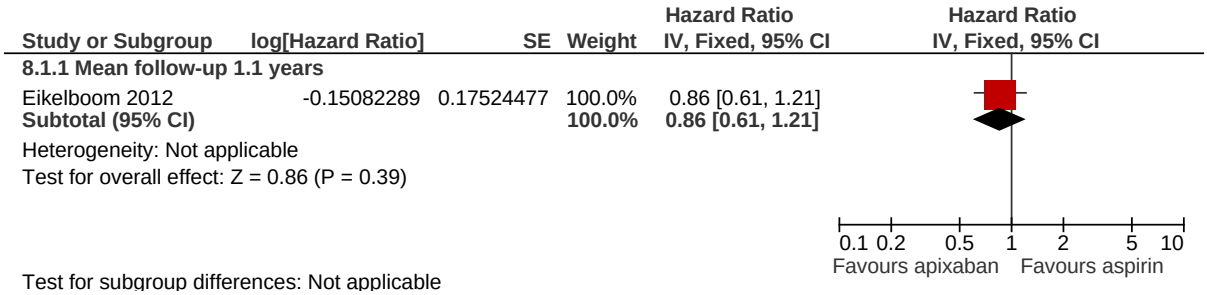
Figure 237: Apixaban versus warfarin in people with atrial fibrillation and eGFR ≤50ml/min/1.73m^2, median follow-up 1.8 years



I.10.6 Apixaban (5mg twice daily) versus aspirin (81-324mg daily)

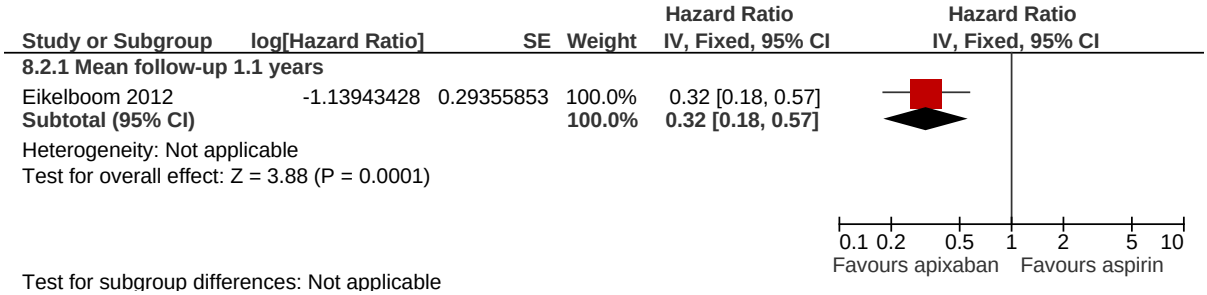
I.10.6.1 All-cause mortality

Figure 238: Apixaban versus aspirin in people with atrial fibrillation, a risk factor for stroke and eGFR 30-59 ml/min/1.73m^2, mean follow-up 1.1 years



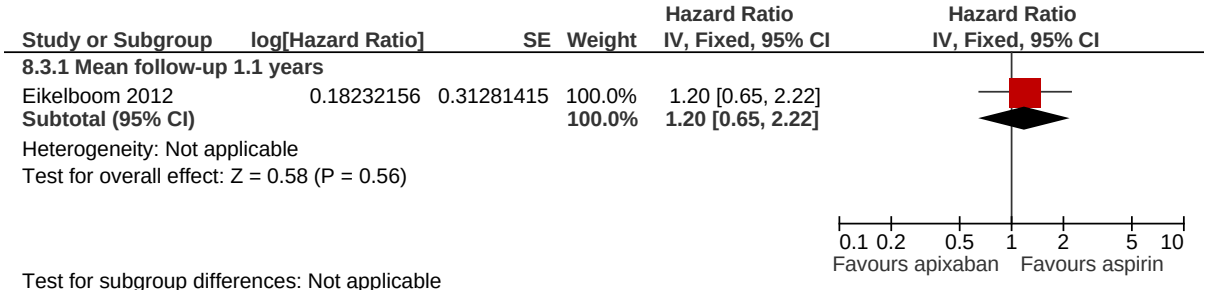
I.10.6.2 Cardiovascular events (stroke or systemic embolism)

Figure 239: Apixaban versus aspirin in people with atrial fibrillation, a risk factor for stroke and eGFR 30-59 ml/min/1.73m^2, mean follow-up 1.1 years



I.10.6.3 Major bleeding (major haemorrhage)

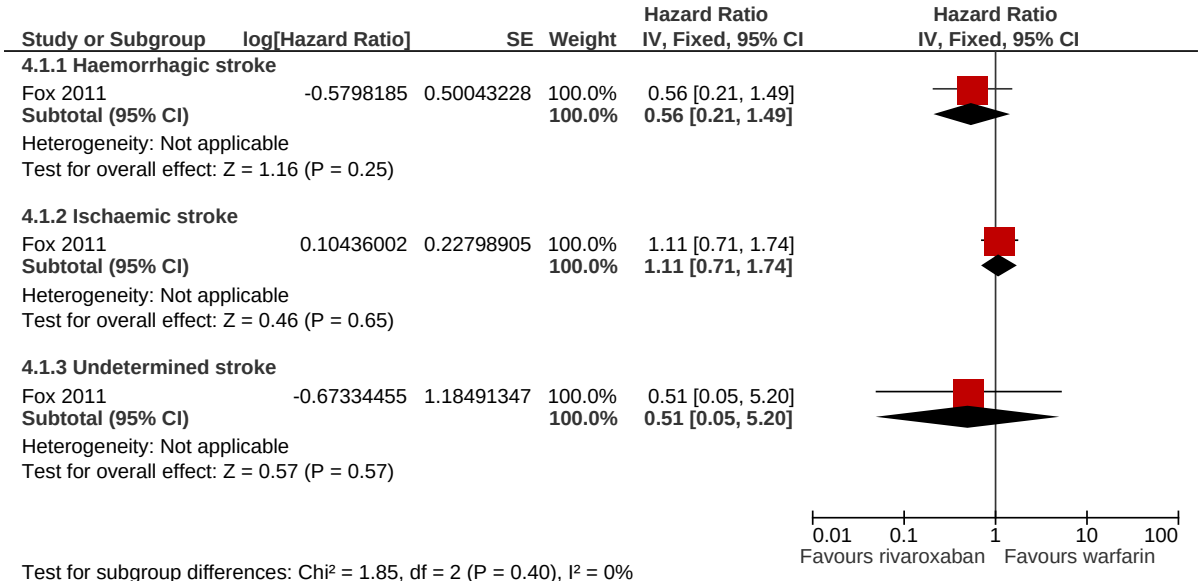
Figure 240: Apixaban versus aspirin in people with atrial fibrillation, a risk factor for stroke and eGFR 30-59 ml/min/1.73m^2, mean follow-up 1.1 years



I.10.7 Rivaroxaban (15mg/day) versus warfarin

I.10.7.1 Cardiovascular events

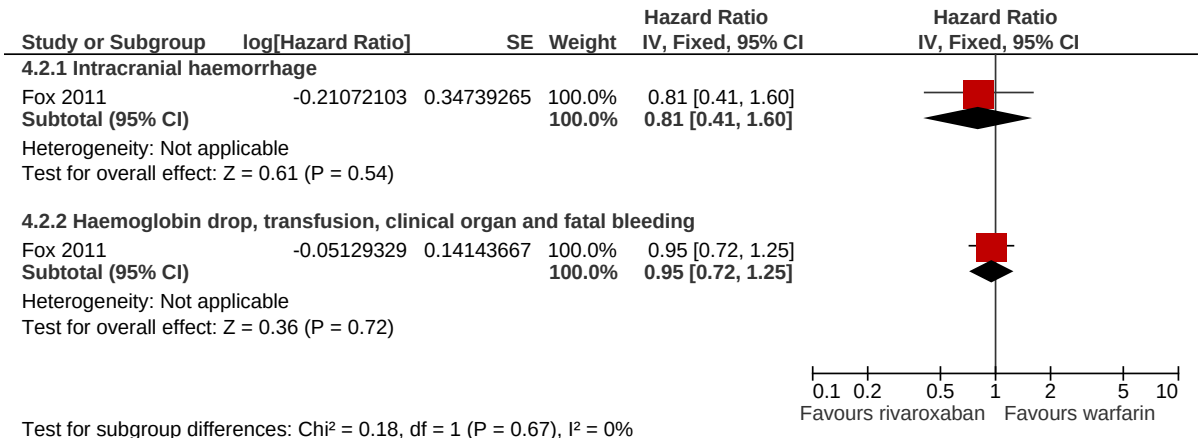
Figure 241: Rivaroxaban versus warfarin in people with atrial fibrillation at moderate to high risk of stroke and CrCl 30-49 ml/min, median follow up 1.9 years



Test for subgroup differences: Chi² = 1.85, df = 2 (P = 0.40), I² = 0%

I.10.7.2 Major bleeding

Figure 242: Rivaroxaban versus warfarin in people with atrial fibrillation at moderate to high risk of stroke and CrCl 30-49 ml/min, median follow up 1.9 years

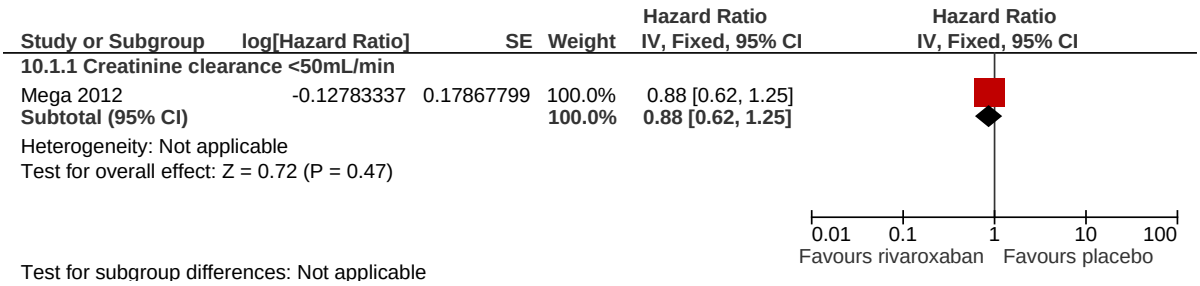


Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

I.10.8 Rivaroxaban versus placebo

I.10.8.1 Cardiovascular mortality, MI or stroke

Figure 243: Rivaroxaban versus placebo in people with a recent acute coronary syndrome



I.10.9 Dabigatran 110 or 150 mg twice daily versus warfarin

I.10.9.1 All-cause mortality

Figure 244: Dabigatran 110mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.

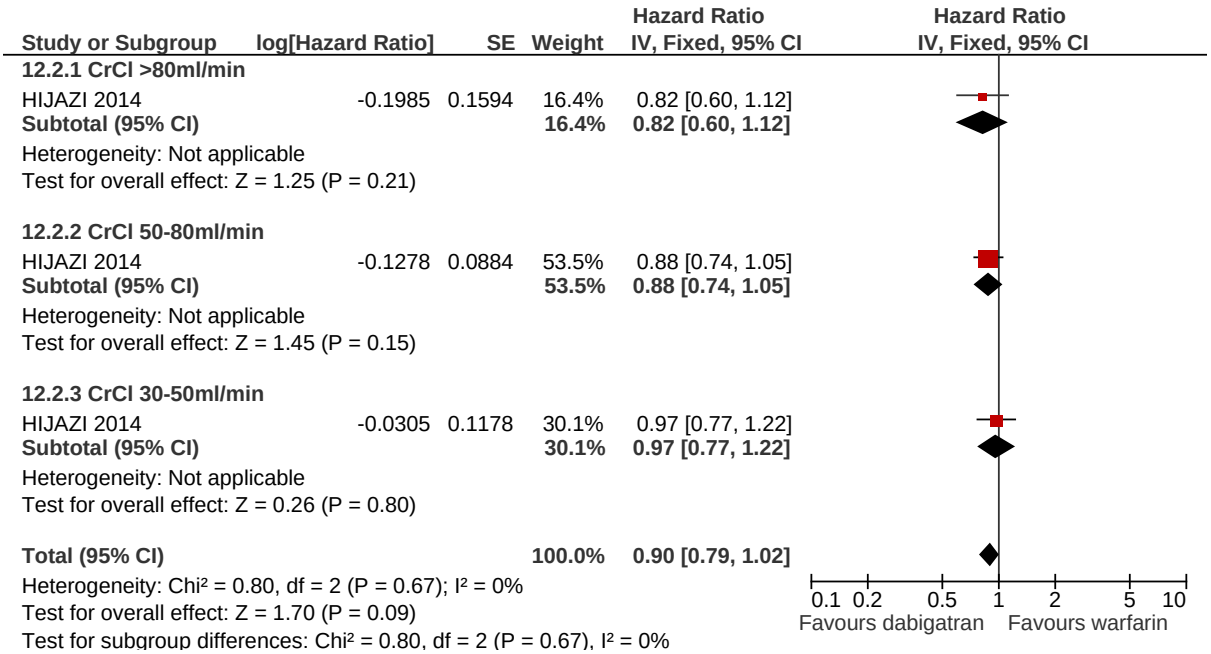
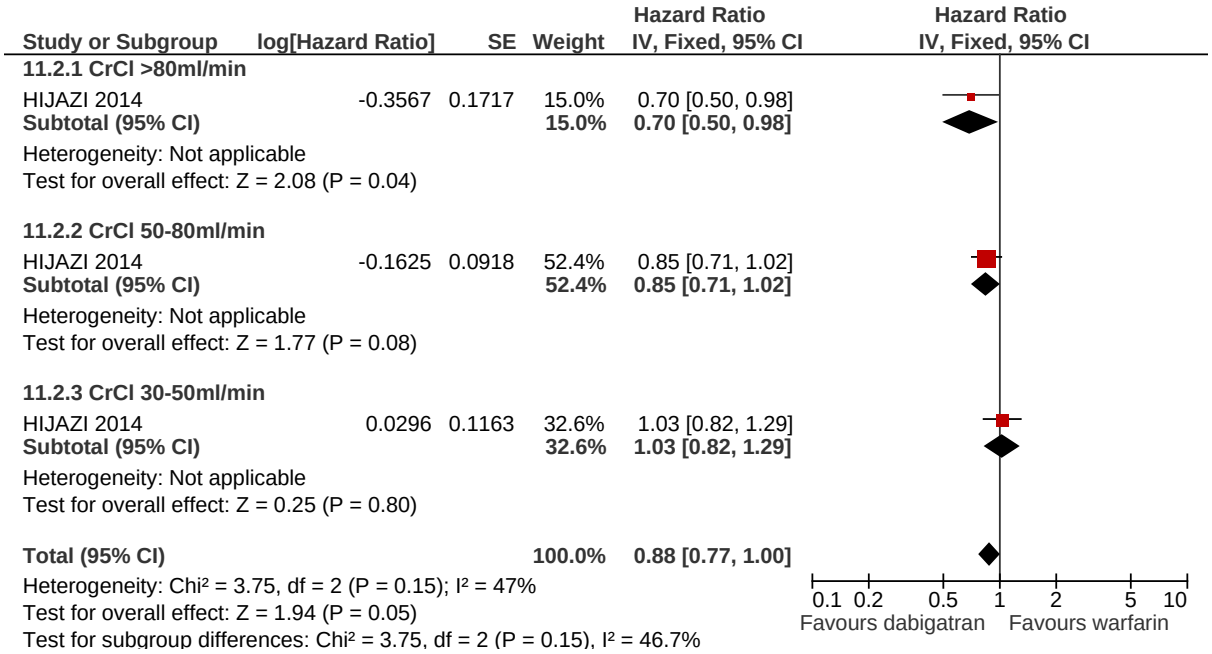


Figure 245: Dabigatran 150mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.



I.10.9.2 Cardiovascular or cerebrovascular events

Figure 246: Dabigatran 110mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.

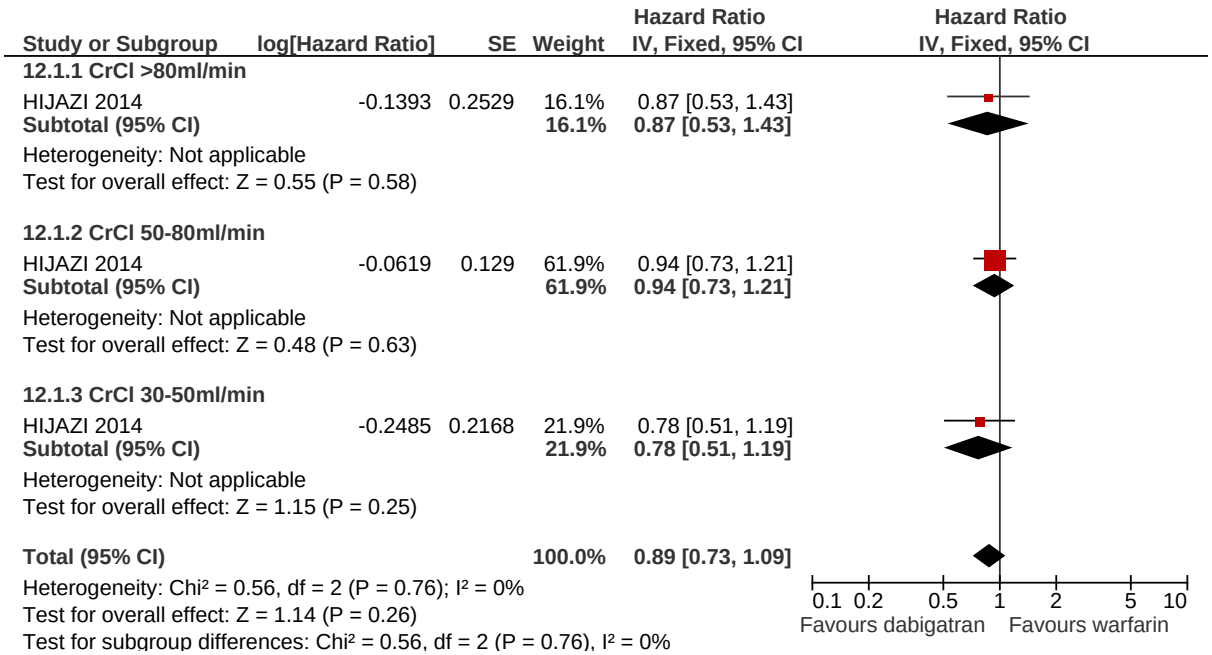
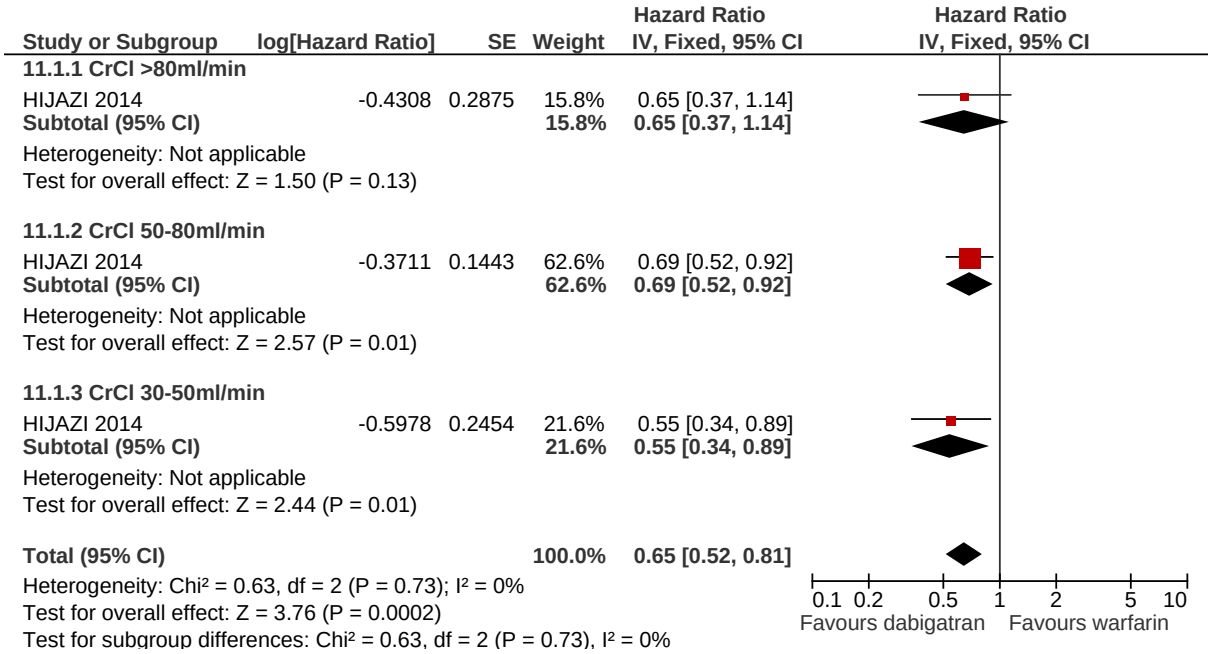


Figure 247: Dabigatran 150mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.



I.10.9.3 Major bleeding

Figure 248: Dabigatran 110mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.

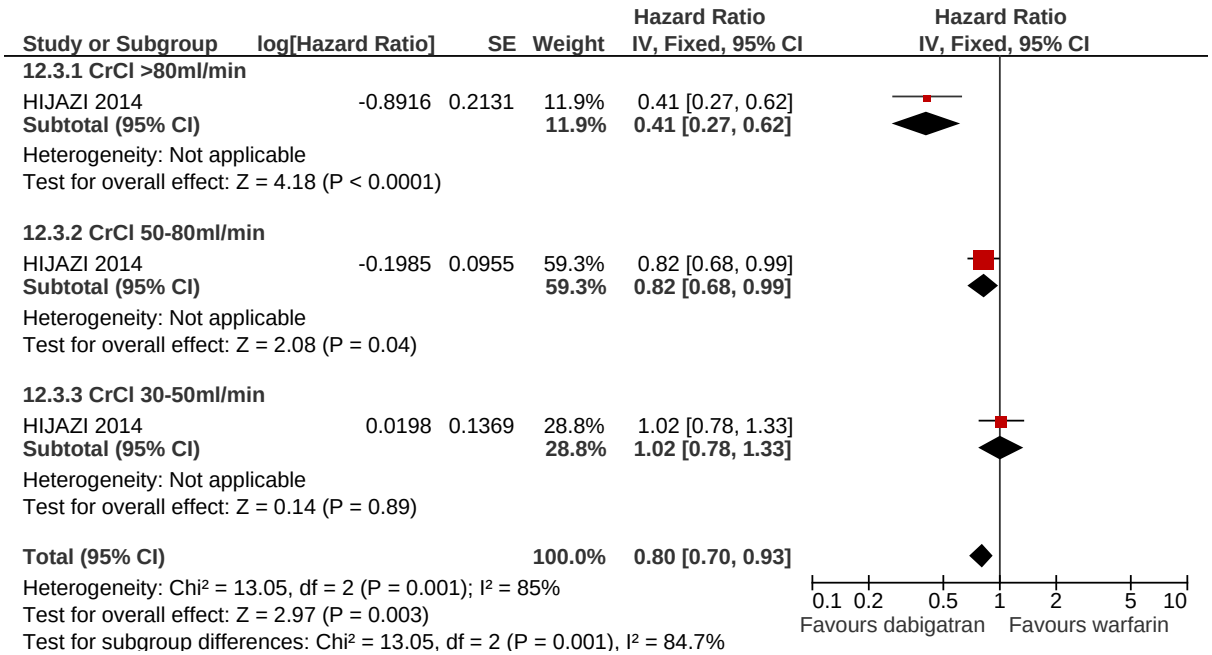
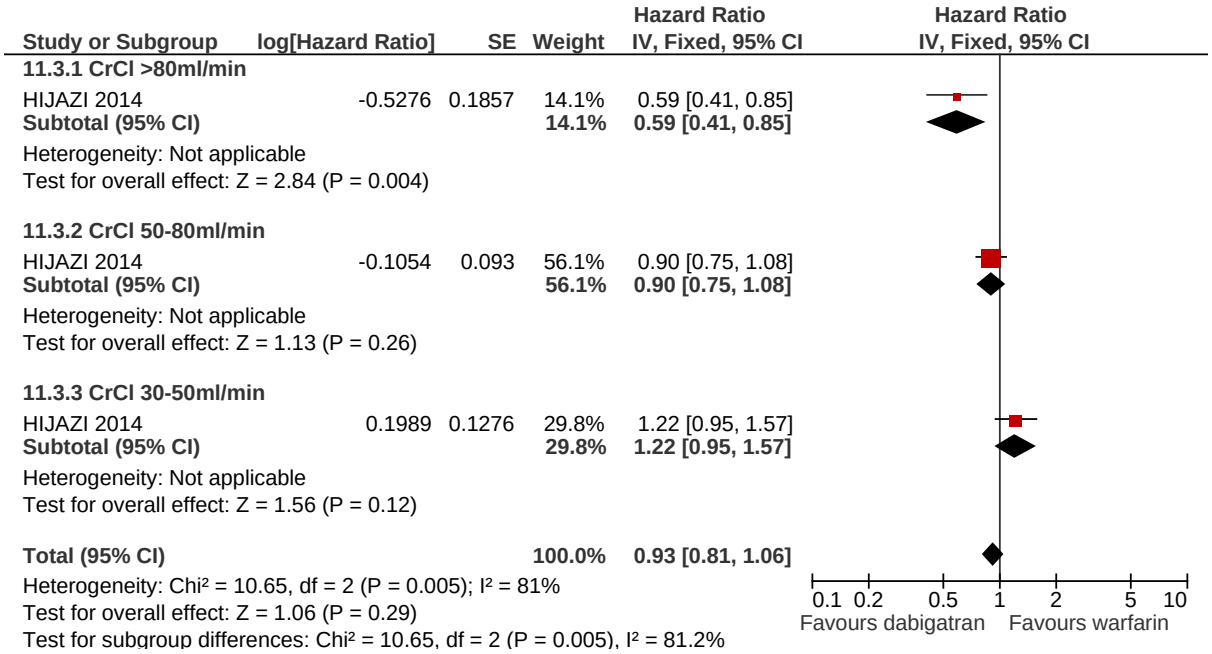


Figure 249: Dabigatran 150mg versus warfarin in people with atrial fibrillation and at least one other risk factor for stroke, median follow up 2 years.



I.11 Asymptomatic hyperuricaemia

I.11.1 Allopurinol compared to usual care in people with CKD and asymptomatic hyperuricaemia

Figure 250: Renal progression (eGFR final values)

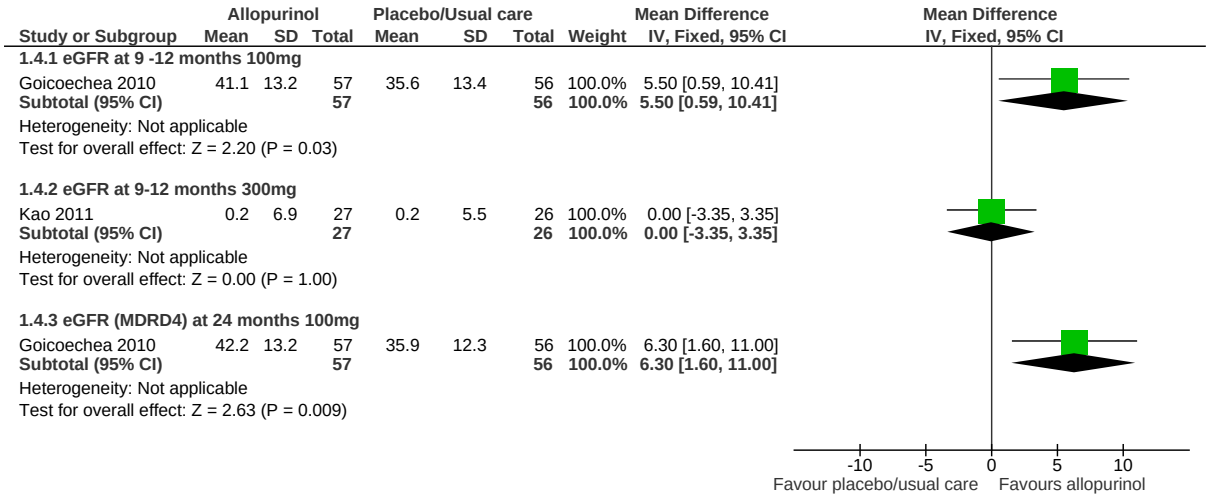


Figure 251: Renal progression (end stage renal disease requiring RRT)

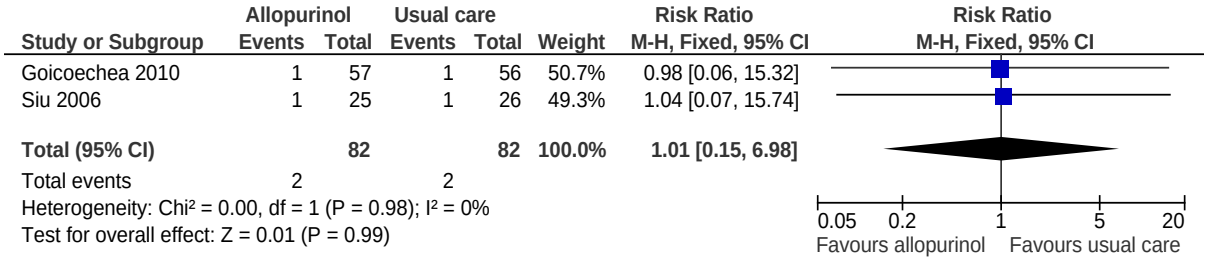


Figure 252: Cardiovascular events

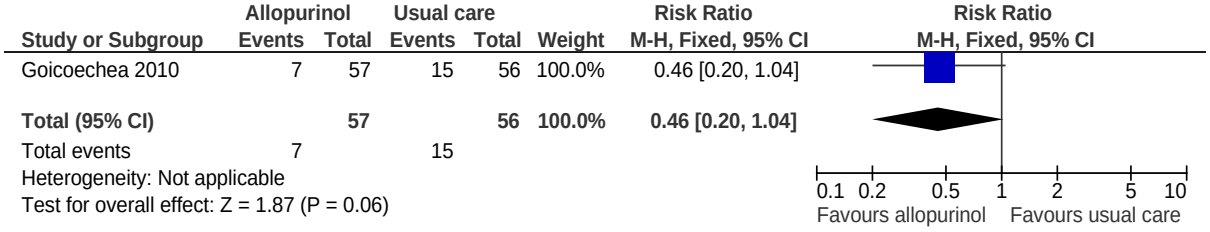


Figure 253: Antihypertensive agents stopped

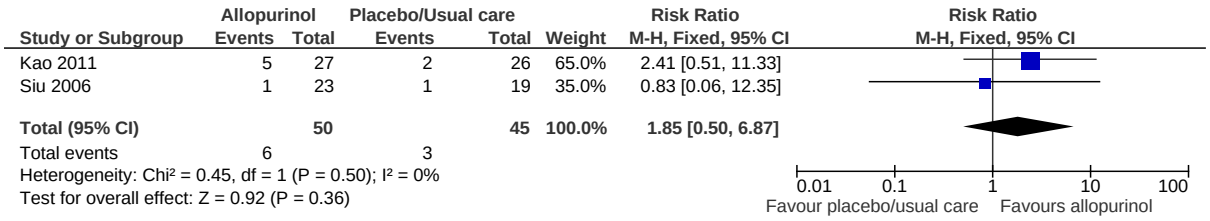


Figure 254: Antihypertensive agents commenced

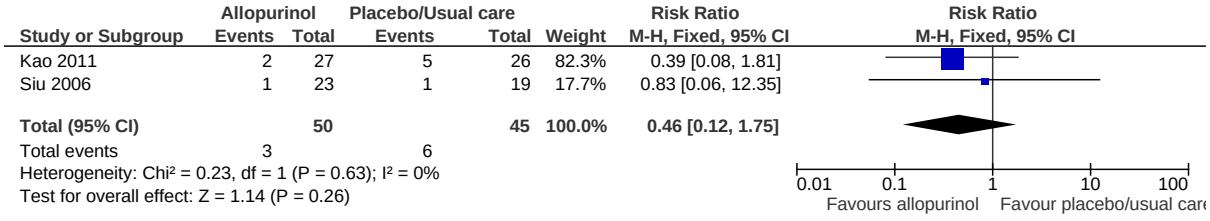


Figure 255: All-cause mortality

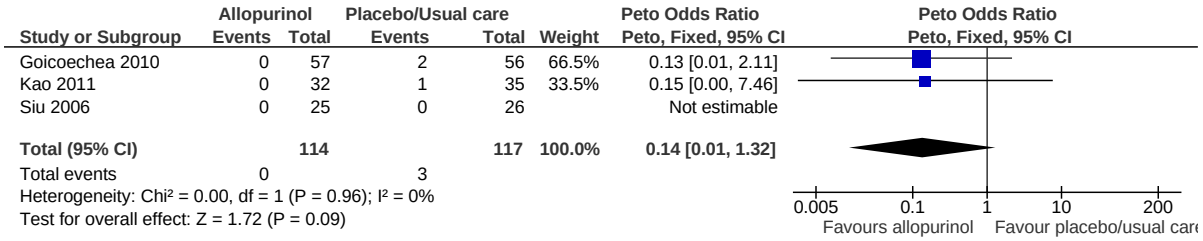
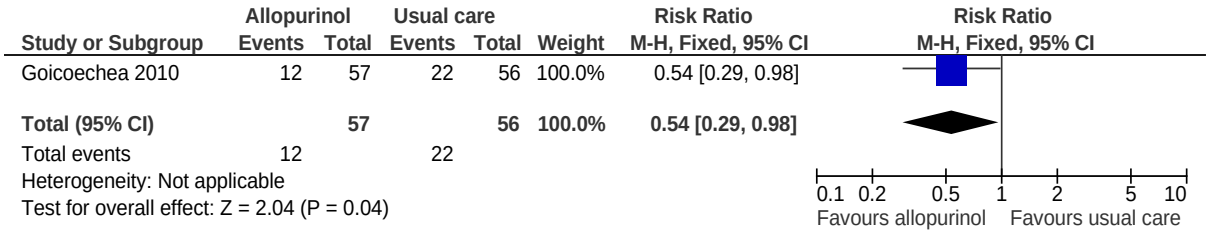


Figure 256: Hospitalisation



I.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

Figure 257: Mortality

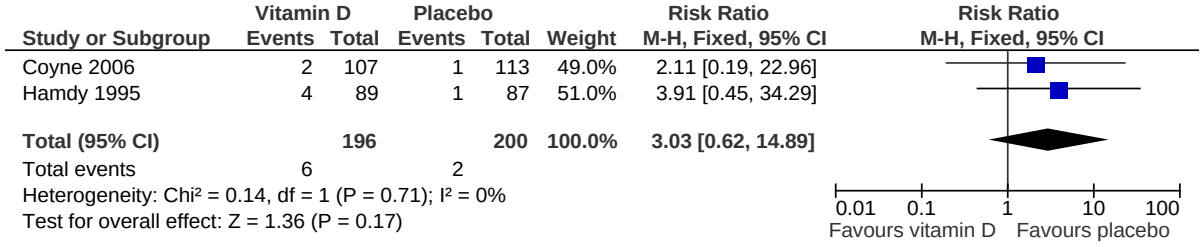


Figure 258: Progression of CKD (GFR)

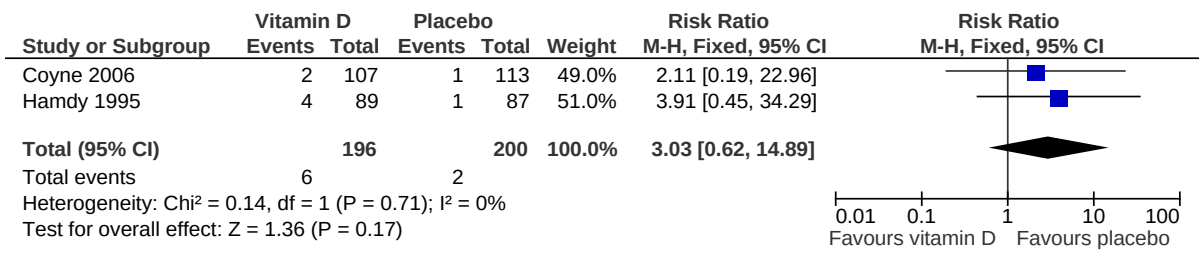


Figure 259: Progression of CKD (creatinine clearance ml/min)

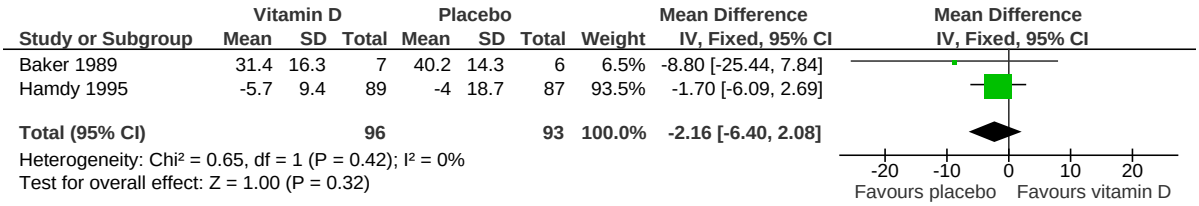


Figure 260: Hypercalcaemia

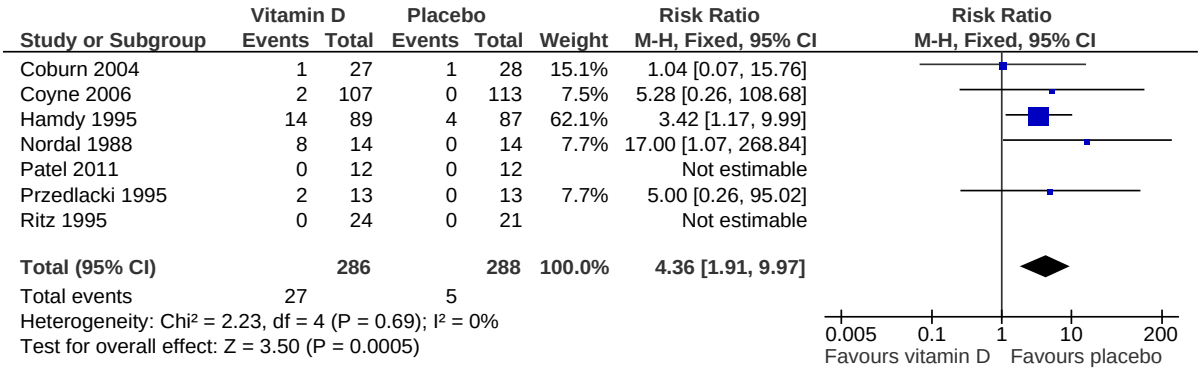


Figure 261: Cardiovascular events

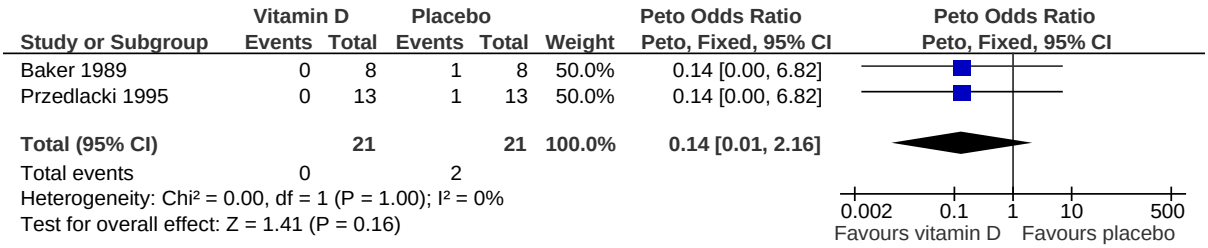
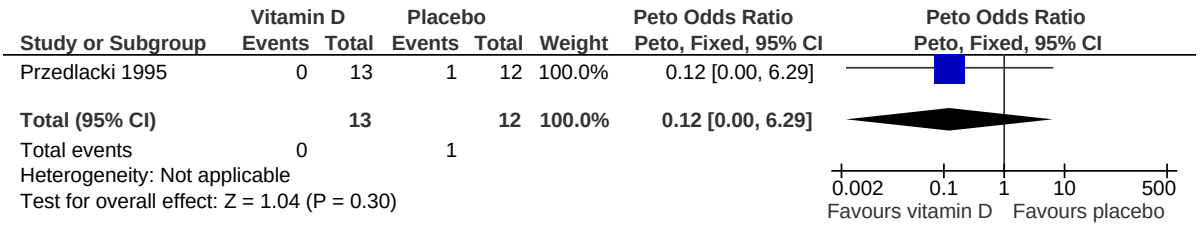


Figure 262: Fracture



I.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

I.13.1 Sodium bicarbonate versus placebo or usual care in the management of CKD

Figure 263: Progression of CKD (measured by change in eGFR)

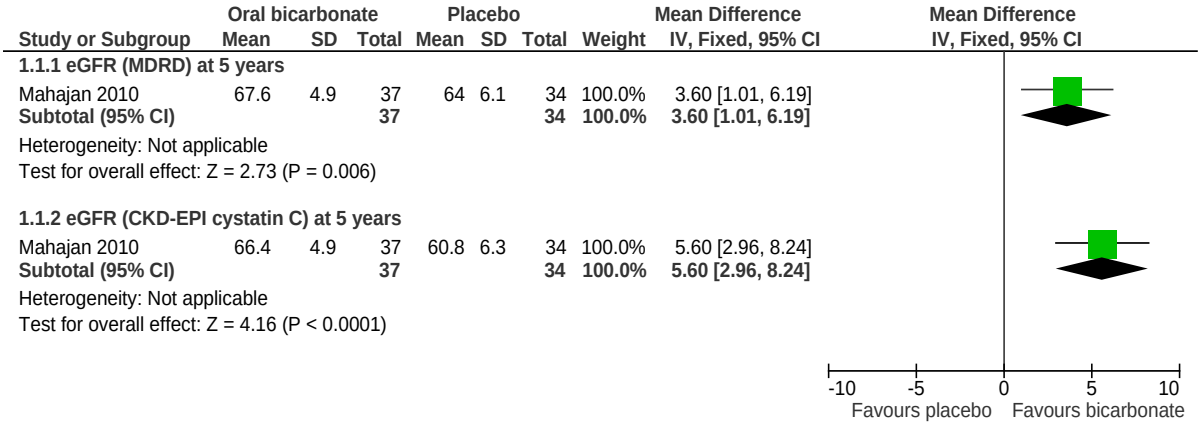


Figure 264: Progression of CKD (measured by end stage renal disease requiring RRT)

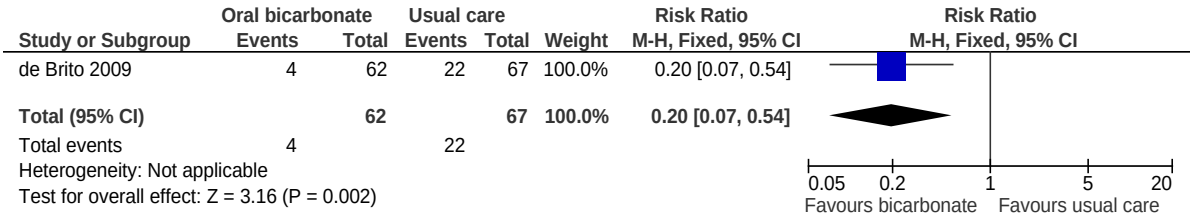


Figure 265: Hypertension (measured by use of antihypertenives)

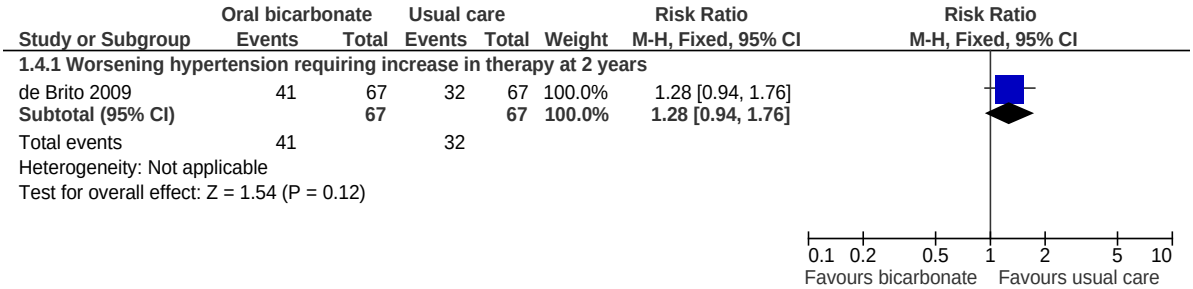


Figure 266: Cardiovascular events (including chronic heart failure)

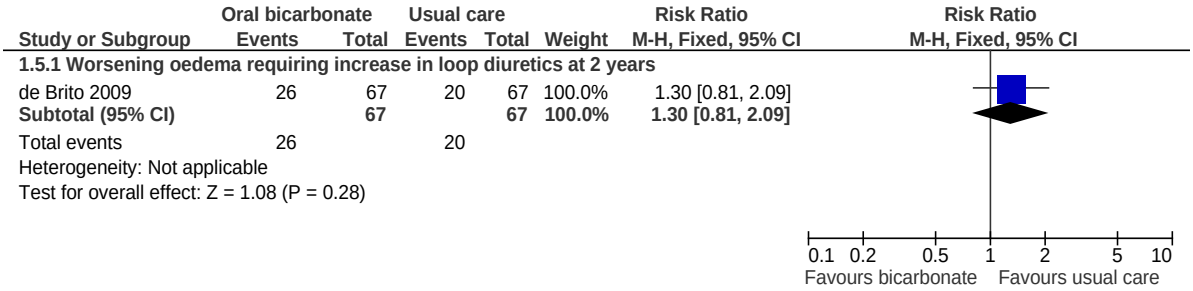
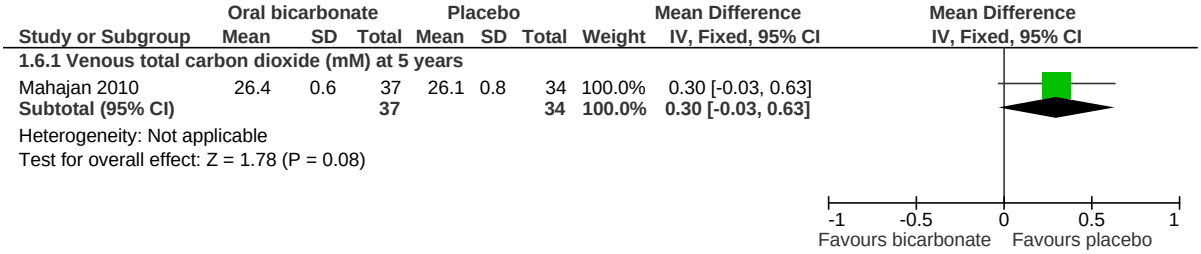


Figure 267: Alkalosis



Appendix J: Excluded clinical studies

J.1 Measuring kidney function

Table 164: Studies excluded from the measuring kidney function clinical review

Reference	Reason for exclusion
Anderson 2012[35]	No external validation of CRIC equation
Bevc 2011[70]	Serum creatinine and cystatin C not internationally standardised
Bevc 2012[71]	Serum creatinine and cystatin C not internationally standardised
Bevc 2012B[69]	Serum creatinine and cystatin C not internationally standardised
Botev 2009[90]	Serum creatinine not internationally standardised
Brown et al 2011[96]	<100 per diagnoses (GFR >60 ml/min/1.73 m^2 vs.GFR <60 ml/min/1.73 m^2)
Camargo 2011[101]	N<100
Carter 2011[106]	No measured GFR
Cha 2010[109]	Population does not match protocol (Korean population only)
Chudleigh 2009[125]	Serum creatinine and cystatin C not internationally standardised
Dowling 2013[168]	Serum creatinine not internationally standardised
Du 2012[173]	Serum creatinine and cystatin C not internationally standardised
Earley 2012[178]	Systematic review, not all studies match protocol. All studies included were checked separately to determine if met with inclusion criteria.
Ebert 2012[179]	Abstract only
Eriksen 2010[187]	Population does not match protocol (general population not people with suspected CKD)
Eriksen 2012[188]	Index tests do not match protocol
Flamant 2012[202]	Abstract only
Fontsere 2006[205]	N<100
Froissart 2005[215]	Serum creatinine not internationally standardised
Grubb 2012[238]	Serum cystatin C not internationally standardised, serum creatinine equation, Lund-Malmo, does not match protocol.
Hallan 2004[241]	Serum creatinine not internationally standardised
Hojs 2008[277]	Index tests do not match protocol
Hossain 2012[280]	Serum creatinine not internationally standardised
Huang 2011[287]	N<100
Ibrahim 2005[289]	Serum creatinine not internationally standardised

Reference	Reason for exclusion
Kallner 2008[325]	Serum creatinine not internationally standardised.
Kallner 2008[326]	Serum creatinine not internationally standardised.
Lee 2009[372]	Serum creatinine not internationally standardised.
Levey 2006[377]	Only one equation that meets protocol in study.
Liu 2013[393]	Geographical, older Chinese peoole only
Ma 2007[402]	Serum creatinine and cystatin C not internationally standardised
MacIsaac 2006[405]	Serum creatinine and cystatin C not internationally standardised
MacIsaac 2007[406]	Serum creatinine and cystatin C not internationally standardised
MacIsaac 2012[404]	Abstract only
Marwyne 2011[426]	Serum creatinine and cystatin C not internationally standardised
Matsuo 2009[433]	Serum creatinine and cystatin C not internationally standardised
Mazza 2010[435]	Serum creatinine not internationally standardised
Nyman 2009 [495]	Serum creatinine index tests do not match protocol and cystatin C not internationally standardised
Oh 2012[509]	Serum creatinine and cystatin C not internationally standardised
Padala et al 2012[515]	Only one equation that meets protocol in study.
Pei 2012[537]	Serum creatinine and cystatin C not internationally standardised
Pei 2013[536]	Serum creatinine and cystatin C not internationally standardised
Poggio 2005[549]	Serum creatinine not internationally standardised
Praditpornsilpa 2011[554]	Population does not match protocol (Thai population only)
Rognant 2011[582]	Serum creatinine not internationally standardised
Saleem 2008[600]	Serum creatinine not internationally standardised
Segarra 2011[621]	Only one equation that meets protocol in study.
Selistre 2012[622]	Serum creatinine not internationally standardised
Stevens 2011[650]	Only one equation that meets protocol in study.
Silveiro 2011[635]	<100 per diagnoses (GFR >60 ml/min/1.73 m^2 vs.GFR <60 ml/min/1.73 m^2)
Tidman 2008[674]	Serum creatinine and cystatin C not internationally standardised
van Deventer 2011[694]	N<100
van Pottelbergh 2010[697]	Systematic review, not all studies match protocol. All studies included were checked separately to determine if met with inclusion criteria.
Xun 2010[729]	Geographical, older Chinese people only

J.2 Markers of kidney damage

Table 165: Studies excluded from the markers of kidney damage clinical review

Reference	Reason for exclusion
Bruno 2007[97]	Creatinine not calibrated to the MDRD methodology
Cirillo 2012[129]	Incorrect intervention (not a combination of measurements: MDRD vs.urinary ACR)
Clase 2011[132]	Not a combination of markers, single marker multivariate model stratified by GFR
Conley 2012[136]	Not a combination of markers, single marker multivariate model stratified by GFR
Matsushita 2012A[434]	Not a combination of markers, single marker multivariate model stratified by GFR
Muntner 2011[461]	Not a combination of markers, single marker multivariate model stratified by GFR
Nerpin 2011[484]	MDRD + urine albumin excretion rate (cystatin C measurement is not standardised)
Rifkin 2010[569]	Not a combination of markers
Smink 2012[639]	Not a combination of markers, single marker multivariate model stratified by GFR
Tonelli 2011[679]	Not a combination of markers
Waheed 2012A[705]	Not a combination of markers, single marker multivariate model stratified by GFR

J.3 Classification of CKD

Table 166: Studies excluded from the classification of CKD clinical review

Reference	Reason for exclusion
Agarwal et al. 2008[14]	Lower quality study* – Regression with eGFR and proteinuria as factors
Agarwal et al. 2012[15]	Lower quality study* - Not stratified by eGFR
Aguilar et al. 2010[20]	Lower quality study*
Alonso et al. 2011[30]	Lower quality study*
Atta et al. 2009[45]	Lower quality study* - Indirect population (people with diabetes)
Baek et al.2012[48]	Lower quality study* - Retrospective cohort
Bello et al. 2011[64]	Lower quality study* - Indirect population (general population)
Berhane et al. 2009[65]	Abstract only
Blecker et al. 2011[84]	Lower quality study* - Indirect population (general population)
Choi et al. 2010[118]	Population not in protocol (people with HIV)
Chronic Kidney Disease	Indirect population (general population)

Reference	Reason for exclusion
Prognosis Consortium 2010[123]	
Deboer et al. 2009[154]	Lower quality study* - Indirect population (people with diabetes)
Drion e al. 2012[171]	Lower quality study* - Indirect population (people with diabetes)
Foster et al. 2007[206]	Lower quality study*
Grams et al. 2010[236]	Lower quality study* - Indirect population (general population)
Groop et al. 2009[237]	Lower quality study* - Indirect population (people with diabetes)
Halbesma et al. 2008[240]	Indirect population (general population), comparison not in protocol (assessment of gender differences only)
Hallan et al. 2009[244]	Lower quality study* - Indirect population (general population)
Hayashi et al. 2010[253]	Lower quality study* - Indirect population (hypertensive)
Hsu et al. 2009[285]	Lower quality study* – Regression with eGFR and proteinuria as factors
Inker et al. 2011[297]	Lower quality study*
Jackson et al. 2009[305]	Lower quality study* - Indirect population (general population)
Le et al. 2012[369]	Lower quality study* - Indirect population (general population)
Leehey et al. 2005[375]	Lower quality study*
Lima et al. 2011[388]	Lower quality study* - Indirect population (stroke)
McManus et al. 2009[439]	Lower quality study* - Indirect population (outpatients with coronary artery disease)
McClellan et al. 2012[437]	Not relevant to protocol – focus on family history of ESRD
Mahmoodi et al. 2012[410]	Indirect population (general population)
Meguro et al. 2009[441]	Lower quality study* - Indirect population (diabetes)
Methven et al. 2011[449]	Lower quality study*
Murussi et al. 2007[463]	Lower quality study* - Indirect population (diabetes)
Ninomiya et al. 2009[488]	Lower quality study* - Indirect population (diabetes)
Norris et al. 2006[491]	Lower quality study*
Obi et al. 2010[503]	Lower quality study* - Retrospective analysis
Ocak et al. 2010[504]	Lower quality study*
Ohare et al. 2010[502]	Lower quality study* - Indirect population (diabetes)
Ohashi et al. 2011[510]	Lower quality study*
Sasso et al. 2012[607]	Lower quality study* - Indirect population (diabetes)
Shastri et al. 2011[628]	Lower quality study* - Indirect population (general population)
Solini et al. 2012[642]	Lower quality study* - Indirect population (diabetes)
Solomon et al. 2007[644]	Lower quality study* - Indirect population (chronic stable coronary disease)
Targher et al. 2011[668]	Lower quality study* - Indirect population (diabetes)
Vlek et al. 2009[702]	Lower quality study* - Indirect population (vascular disease)
Warnock et al. 2010[713]	Lower quality study* - Indirect population (stroke)
Wu et al. 2012[727]	Lower quality study*
Yang et al. 2007[731]	Lower quality study* - Indirect population (diabetes)

Reference	Reason for exclusion
Yang et al. 2008[732]	Lower quality study* - Indirect population (diabetes)
Yokoyama et al. 2011[735]	Abstract only
Yokoyama et al. 2012[734]	Lower quality study* - Indirect population (diabetes)
Yoshida et al. 2008[736]	Lower quality study* – Regression with eGFR and proteinuria as factors
Zambon et al. 2012[737]	Not relevant to protocol – compares sex differences only

* Lower quality study compared to IPD meta-analysis

J.4 Cause of CKD – risk of adverse outcomes

J.4.1 Glomerular disease

Table 167: Studies excluded from the clinical review – glomerular disease

Study	Exclusion reason
Dumoulin et al. 2003[176]	Does not meet review protocol.
Ekart et al. 2013[181]	Retrospective, only considers people who progressed to RRT.
Heeringa et al. 2007[257]	Does not meet review protocol.
Hladunewich et al. 2009[270]	Does not meet review protocol (analysis of nephrotic versus sub-nephrotic).
Hoefield et al 2013[273]	Does not meet review protocol, glomerular disease if the reference group.
Lee et al. 2012[373]	Compares high and low risk patients rather than types of glomerular disease or glomerular disease versus no glomerular disease.
Lv et al 2013[401]	Systematic review – references checked for inclusion.

J.4.2 Acute kidney injury

Table 168: Studies excluded from the clinical review – acute kidney injury

Study	Exclusion reason
Ahlstrom et al. 2005[21]	Not guideline population (people on dialysis)
Bagshaw et al. 2005[49]	Does not meet review protocol.
Bedford et al. 2012[63]	Editorial
Bucaloiu et al. 2012[98]	Inappropriate study design (case control study)
Coca et al. 2011[135]	Systematic review – references checked for inclusion.
Coca et al. 2012[134]	Systematic review – references checked for inclusion.
Goldberg et al. 2008[231]	Systematic review – references checked for inclusion.
Grams et al. 2010[236]	Does not meet review protocol.
Hsu et al. 2009[284]	All occurrences of AKI were when CKD was already present.

Study	Exclusion reason
Hsu et al. 2011[286]	Systematic review – references checked for inclusion.
Ishani et al. 2009[304]	Cohort starts with all people with ESRD rather than people with AKI who develop ESRD.
Liano et al. 2007[387]	Does not meet review protocol.
Lins et al. 2006[392]	Does not meet review protocol.
Loef et al. 2005[398]	Indirect population (post-operative).
Morgera et al. 2002[457]	Does not meet review protocol.
Siew et al. 2012[634]	Does not meet review protocol.

J.5 Frequency of monitoring

Table 169: Studies excluded from the frequency of monitoring clinical review

Reference	Reason for exclusion
Abdelhafiz et al 2012[9]	No UK loan locations- order cancelled
Alaly et al 2010[26]	CKD in RA Veterans population only
Ali et al 2013[29]	Does not match protocol
Altemtam et al 2012[31]	Does not match protocol
Astor2011[43]	Does not match protocol
Babayev2013[46]	No adjusted HR reported
Baek2012[48]	Does not match protocol
Barbour et al 2010[57]	Systematic review not all studies meet PICO, all studies assessed individually.
Berhane et al 2011[66]	Does not match protocol
Boudville et al 2012[91]	Does not match protocol
Clark et al 2011[131]	Does not match protocol
Conley et al 2012[136]	Does not match protocol
Erickson et al 2013[185]	Does not match protocol; no adjusted HR reported - univariate analysis only.
Hallan et al 2009[244]	Does not match protocol
Hemmelgarn et al 2007[259]	Does not match protocol
Hemmelgarn et al 2010[261]	Does not match protocol
Heras et al 2012[264]	Does not match protocol
Hoefield et al 2011[272]	Does not match protocol
Khatami et al 2007[337]	Does not match protocol
Khedr et al 2011[338]	Does not match protocol
Leehey et al 2005[375]	Does not match protocol
Li et al 2012[385]	Does not match protocol

Reference	Reason for exclusion
Madero et al 2007[407]	Does not match protocol
Molitch et al 2010[455]	Does not match protocol
Murussi et al 2007[463]	Does not match protocol
Nitsch et al 2013[489]	Does not match protocol
Obi et al 2010[503]	Does not match protocol
O'Hare et al 2012[501]	Adjusted HR only reported for population after RRT started
Ohashi et al 2011[510]	Does not match protocol. Hospitalised CKD only, therefore not monitoring in general population of people with CKD.
Othman et al 2009[514]	Does not match protocol
Schmieder et al 2011[616]	Indirect population (not CKD)
Selvin et al 2013[623]	Does not match protocol
Soares et al 2009[641]	Not review population (paediatric)
Tangri et al 2011[667]	Does not match protocol
Tseng et al 2012[683]	Abstract only
Turin et al 2013[684]	No 95% CI reported
Unsal et al 2012[691]	Does not match protocol
Vandervelde et al 2011[693]	Does not match protocol
Vupputuri et al 2011[704]	Does not match protocol; univariate analysis only.
Yoshida et al 2008[736]	Does not match protocol

J.6 Progression of CKD after acute kidney injury

Table 170: Studies excluded from the CKD progression after AKI clinical review

Reference	Reason for exclusion
Chawla 2011[114]	Incorrect study design (derivation of risk models for CKD4)
James 2010B[310]	Superseded by James 2011B[309] which also reports Hazard Ratios for same population.
Gansevoort 2011[218]	AKI is the outcome studied not the risk factor for ESRD or CKD progression
Ponte 2008[550]	Incorrect study design (derivation of model to predict GFR during follow-up)
Schiffl 2006[613]	Incorrect study design (case series)

J.7 Low protein diets

Table 171: Studies excluded from the low protein diet clinical review

Study	Exclusion reason
Campbell 2008[102]	Less than minimum duration
Di iorio 2003[164]	Incorrect interventions
Dullaart 1993[175]	Not guideline condition
Dussol 2005[177]	Incorrect interventions
Fouque 2006[207]	Systematic review. Relevant studies included.
Hansen 2002[246]	Incorrect interventions
Ihle 1989[290]	Incorrect interventions
Jungers 1987[322]	Incorrect interventions
Koya 2009[356]	Incorrect interventions
Malvy 1999[415]	Incorrect interventions
Menon 2009[448]	Incorrect interventions
Mircescu 2007[453]	Incorrect interventions
Pan 2008[522]	Systematic review is not relevant to review question or unclear PICO
Pedrini 1996[535]	Systematic review : all studies included in Cochrane reviews
Pijls 2002[548]	Not guideline condition
Robertson 2007[576]	Systematic review. Relevant studies included.
Sanchez 2010[602]	Less than minimum duration
Tangri 2011[667]	Post hoc subgroup analysis
Teplan 2010[671]	Abstract of post hoc analysis
Yasuda 2010[733]	Crossover study

J.8 Self-management

Table 172: Studies excluded from the clinical review

Reference	Reason for exclusion
Sabariego 2010[598]	Education program, not relevant to protocol.
Thomas 2013[673]	Not guideline population. Not relevant to protocol.

J.9 Blood pressure - combined renin-angiotensin-aldosterone system antagonists

Table 173: Excluded studies from clinical review: For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone antagonists in the management of CKD?

Study	Exclusion reason
Agarwal 2011[16]	Not review population. Systematic review, subgroup with CKD, relevant papers included.
Agodoa 2001[19]	Incorrect interventions. ramipril vs. amlodipine
Anon 2000[3]	Not guideline condition
Appel 2010[37]	Incorrect interventions
Atmaca 2006[44]	Fewer than 30 people
Bakris 1992[53]	Incorrect interventions. lisinopril vs. verampamil vs. diuretic
Bakris 1994[54]	Fewer than 30 people
Barnett 2006[58]	No additional material over Barnett 2004
Bhavsar 2011[73]	Incorrect interventions
Bianchi 2006[74]	Incorrect interventions. Open label study with 'conventional care' as comparator
Bianchi 2010[75]	Incorrect interventions
Bichu 2009[76]	Review not main trial
Bilous 2009[79]	Not guideline condition
Bilous 2010[80]	Not guideline condition
Blacklock 2011[83]	All eligible studies included separately (includes some we excluded). Less than minimum duration
Bomback 2008[87]	Not RCT
Brouwers 2011[95]	Incorrect study design. non-randomised extension study
Capek 1994[103]	Less than 30 people
Carella 1999[104]	Crossover study
Casas 2005[107]	Systematic review is not relevant to review question or unclear PICO. comparison is ACE inhibitors or ARB versus other antihypertensives
Chase 1993[113]	Fewer than 30 people
Chrysostomou 2006[124]	Less than minimum duration
Cordonnier 1999[138]	Fewer than 30 people
Daien 2012[148]	Not guideline condition
Dalla 2004[149]	Incorrect interventions. wrong comparison: ramipril vs. lercanidipine
Davidson 2011[152]	Incorrect interventions
Epstein 2006[184]	Less than minimum duration
Estacio 1996[192]	Incorrect interventions. not our comparisons: enalapril vs. Nisoldipine
Estacio 1998[193]	Incorrect interventions. not our comparisons: enalapril vs. Nisoldipine

Estacio 1998[191]	Incorrect interventions. enalapril vs. nisoldipine
Estacio 2000[190]	Incorrect interventions. enalapril vs. nisoldipine
Esteghamati 2013[194]	Open label trial with participants who are already receving the study drugs.
Evans 2009[195]	Abstract only
Evans 2012[196]	Incorrect interventions
Fan 2006[198]	Incorrect interventions
Fernandez-juarez 2006[200]	Less than minimum duration
Fried 2009[212]	Inappropriate comparison. design only no outcomes
Furumatsu 2008[216]	Incorrect interventions. spironolactone + ACE inhibitors + ARB vs. diuretic + ACE inhibitors + ARB
Garg 1998[222]	Not guideline condition. not all patients had CKD
Hansen 1994[247]	Fewer than 30 people
Hansen 1995[248]	Incorrect interventions. captopril + bendrofluazide vs. no treatment
Hellemons 2011[258]	Post hoc analysis - evaluates the slope of renal function loss. Less than minimum duration
Hirst 2012[269]	Not RCT
Horita 2006[279]	Incorrect interventions. intervention is temocapril (not on list)
Hou 2007[281]	Incorrect interventions. 2 doses same drug versus drug not on list
Imai 2006[296]	Inappropriate comparison. design only no outcomes
Imai 2010[293]	Abstract only - all in Imai 2011A
Imai 2012[295]	Abstract only all in Imai 2011A
Jafar 2001[307]	Systematic review is not relevant to review question or unclear PICO. most studies wrong intervention/comparison
Jafar 2007[306]	Incorrect interventions. ordered in error
Jennings 2007[316]	Not RCT
Jerums 2001[318]	Fewer than 30 people
Jun 2011[321]	Systematic review: methods are not adequate/unclear. review - not systematic
Kahvecioglu 2007[324]	Fewer than 30 people
Kent 2007[335]	Systematic review is not relevant to review question or unclear PICO. pooled analysis ACE inhibitors + antihypertensives vs. antihypertensives; not SR
Kim-mitsuyama 2013[342]	Incorrect interventions. Inappropriate comparison
Knudsen 2008[347]	Not guideline condition
Ko 2005[348]	Not guideline condition. not all patients had CKD
Kosmadakis 2010[354]	Fewer than 30 people
Kunz 2008[359]	Not RCT
Lea 2005[370]	Incorrect interventions. ramipril vs. metoprolol vs. amlodipine
Lee 2011[374]	Incorrect interventions. Comparator - usual antihypertensive therapy (i.e. no placebo)

Lizakowski 2013[394]	Crossover study. Less than minimum duration
Locatelli 1997[397]	Incorrect study design. non-randomised extension study
Lv 2012[400]	Not guideline condition
Maione 2007[413]	Inappropriate comparison. design of study only - no outcomes
Maione 2011[412]	Not RCT
Mann 2008[418]	Not guideline condition
Mann 2013[419]	Compares with dual therapy with monotherapy which could either be ramipril or telmisartan.
Marin 2001[420]	Incorrect interventions. wrong comparison - fosinopril vs. nifedipine
Marre 1987[424]	Less than minimum duration
Marre 1988[423]	Fewer than 30 people
Marre 1990[422]	Fewer than 30 people
Maschio 1996[427]	Incorrect interventions. benazepril
Maschio 1999[428]	Incorrect interventions. benazepril not listed
Mathiesen 1991[429]	Incorrect interventions. captopril + diuretic vs. no treatment
Mathiesen 1999[430]	Incorrect interventions. captopril + diuretic vs. no treatment
Matsuda 2003[432]	Less than minimum duration
Mehdi 2009[442]	Less than minimum duration
Mehler 2003[443]	Incorrect interventions. enalapril vs. nisoldipine
Mimura 2008[452]	Incorrect study design
Mori-takeyama 2008[458]	Incorrect interventions
Navaneethan 2009[483]	Systematic review, all relevant studies included.
O'donnell 1993[496]	Less than minimum duration
Ogawa 2007[507]	Incorrect interventions
Oguri 2009[508]	Fewer than 30 people
Parving 1989[525]	Incorrect interventions. no treatment control group
Parving 2001[524]	Non-English language
Parving 2001[526]	Incorrect interventions. no treatment control group
Parving 2008[528]	Less than minimum duration
Parving 2009[529]	Inappropriate comparison. design of study only no outcomes
Parving 2012[530]	Inappropriate comparison. baseline characteristics only no outcomes
Perkovic 2007[540]	Incorrect interventions. perindopril + indapamide vs. placebo + indapamide
Pham 2011[545]	Not RCT
Phillips 1993[546]	Less than minimum duration
Poulsen 2001[553]	Pooled data from 2 RCTs. 1 included. 1 excluded
Poulsen 2001[552]	No outcomes relevant to protocol (albuminuria during exercise)
Rahman 2006[561]	Incorrect interventions
Ravid 1993[563]	Incorrect study design. commentary not original study

Ravid 1995[565]	Inappropriate comparison. no relevant outcomes
Ravid 1996[564]	Incorrect study design. non-randomised extension study
Remuzzi 1991[568]	Inappropriate comparison. no comparison reported - study design only no outcomes
Rizos 2012[574]	Not RCT
Rizzoni 2005[575]	Not guideline condition
Romero 1993[583]	Less than minimum duration. Incorrect interventions
Ros-ruiz 2012[584]	Incorrect study design
Rossing 2005[588]	Less than minimum duration
Ruggenenti 1998[593]	Incorrect interventions. effect of CCB
Ruggenenti 1998[595]	Incorrect study design. non-randomised follow up study
Ruggenenti 2001[596]	Duplicates Gisen 1997 [ID2851] and Ruggenenti 1999 [2853]
Sano 1994[605]	Incorrect interventions. "no treatment" control group
Sano 1996[604]	Incorrect interventions. "no treatment" control. not placebo or RAAS
Sarafidis 2008[606]	Not RCT
Sato 2003[608]	Incorrect study design
Savage 1996[610]	Incorrect study design. cohort study
Schjoedt 2005[614]	Crossover study
Schjoedt 2006[615]	Crossover study
Schrier 1996[617]	Incorrect interventions. wrong comparison - enalapril vs. nisoldipine
Schrier 2002[618]	Incorrect interventions. enalapril vs. nisoldipine
Sengul 2006[624]	Less than minimum duration
Shahinfar 2002[626]	No outcomes relevant to review protocol
Sharma 2011[627]	Systematic review - all papers included.
Shoda 2006[632]	Incorrect interventions
Stornello 1989[654]	Less than minimum duration
Stornello 1992[655]	Crossover study
Strippoli 2006[657]	Not RCT
Tamura 2008[664]	Incorrect interventions
Tan 2002[665]	Less than minimum duration
Tang 2012[666]	Incorrect study design
Toth 2010[681]	Summary/commentary not original RCT
Trevisan 1995[682]	Less than minimum duration
Tylicki 2007[689]	Not guideline condition
Tylicki 2008[688]	Less than minimum duration
Vejakama 2012[699]	Not RCT
Wang 2009[711]	Not RCT
Winkelmayer 2006[723]	Age-specific subgroup analysis but not >75 years
Wright 2002[725]	Incorrect interventions

Yanagi 2013[730]	Inappropriate comparison. Less than minimum duration
Zannad 2006[738]	Dialysis patients

J.10 Oral anticoagulants and antiplatelets

Table 174: What is the efficacy and safety of antiplatelet and antithrombotic therapy

Study	Exclusion reason
Ahmed 2011[24]	Less than minimum duration. Outcomes only reported at 30 days.
Anon 2010[8]	Incorrect study design. Trial rational and resign only.
Baigent 2005[50]	Inappropriate comparison. Simvastatin. Dialysis patients
Becker 2011[61]	Duplicate of data reported in James et al. 2010
Bhatt 2006[72]	No CKD subgroup. Not guideline condition
Connolly 2009[137]	Not guideline condition. No CKD subgroup.
Dahl 2012[147]	Not guideline condition. Inappropriate comparison. Incorrect interventions. Dabigatran versus enoxaparin. People aged over 75 or those with renal impairment. Not separated for analysis.
Dash 2013[151]	Less than minimum duration
Diener 2008[165]	Not guideline condition. Not review population. No CKD subgroup
Engelbertz 2012[182]	Not systematic review or RCT
Giannitsis 2012[225]	Summary of all subgroup analysis. Data reported in James et al.2010
Hansson 1998[249]	Not guideline condition. Not CKD subgroup
Hart 2011[252]	Incorrect interventions. Fixed dose warfarin combined with aspirin - not relevant to clinical practice.
Hart 2011[251]	Abstract
Healey 2010[255]	Abstract
Hori 2013[278]	Subgroup analysis of ROCKET AF only reporting Japanese trial data.. Data reported in Fox et al.
Hughes 2012[288]	Not guideline condition. Not review population. No CKD subgroup.
James 2009[311]	Not guideline condition. Not CKD population; design of study only
James 2011[313]	Abstract
Jardine 2010[314]	Abstract only - full paper included
Jun 2011[321]	Not RCT
Mehran 2009[444]	Inappropriate comparison. Incorrect interventions
Mehta 2000[445]	Not guideline condition. Not review population. No CKD subgroup.
Ogawa 2008[506]	Not guideline condition. No CKD subgroup
Palmer 2012[520]	Not RCT
Patel 2011[533]	No CKD subgroup. Not guideline condition. Not review population
Piccini 2013[547]	Re-analysis of data presented in Fox et al. . Data analysis not relevant to protocol.

Study	Exclusion reason
Poulsen 2012[551]	Review - references checked for relevant studies.
Pride 2009[556]	Not guideline condition. Not review population. No CKD subgroup.
Saito 2011[599]	Aspirin versus no aspirin (not placebo). Inappropriate comparison. Incorrect interventions
Saltzman 2011[601]	Inappropriate comparison. Incorrect interventions
Schulman 2013[619]	Not guideline condition. No CKD subgroup
Steinhubl 2002[649]	Not guideline condition. Not review population
Suh 2011[658]	Not guideline condition. Not review population
Tobbia 2011[675]	Incorrect interventions. Abstract only.
Wallentin 2009[709]	Not guideline condition. No CKD subgroup
Wallentin 2013[710]	Not guideline condition. No CKD subgroup
Weimar 2012[716]	Not guideline condition. Not review population. No CKD subgroup.

J.11 Asymptomatic hyperuricaemia

Table 175: Studies excluded from the clinical review

Study	Exclusion reason
Agarwal 2011[16]	Abstract only and includes studie sthat do not match PICO
Momeni 2010[456]	Population does not match protocol

J.12 Vitamin D supplements in the management of CKD-mineral and bone disorders

Table 176: Studies excluded from the Vitamin D clinical review

Study	Exclusion reason
Adachi 2011[11]	Dialysis patients
Aggarwal 2011[17]	Less than minimum duration
Alborzi 2008[27]	Less than minimum duration
Alvarez 2012[32]	No outcomes relevant to the protocol
Bjorkman 2009[82]	Systematic review is not relevant to review question or unclear PICO
Bosworth 2012[89]	No outcomes relevant to the protocol
Chandra 2008[112]	Less than minimum duration
Cheng 2012[116]	Dialysis patients
Christiansen 1978[122]	No outcomes relevant to the protocol
De boer 2010[153]	abstract only
De zeeuw 2010[159]	12% had eGFR >60 ml/min/1.73 m^2. Not review population

Study	Exclusion reason
Dogan 2008[167]	open label study
Drueke 2009[172]	review not systematic
Fishbane 2009[201]	eGFR 15-90 ml/min/1.73 m^2. Not review population
Garside 2007[223]	Intervention not in protocol (cinacalcet). Incorrect interventions
Giustia 2009[228]	abstract only
Kooienga 2009[351]	No outcomes relevant to the protocol
Koshikawa 2002[353]	Dialysis patients
Kovesdy 2012[355]	Less than minimum duration
Krairittichai 2012[357]	Less than minimum duration
Moe 2010[454]	Less than minimum duration
Oksa 2008[511]	open label study
Palmer 2009[521]	systematic review not all papers relevant. Systematic review is not relevant to review question or unclear PICO
Petchey 2009[542]	Protocol only
Petchey 2013[544]	No outcomes relevant to the protocol
Petchey 2013[543]	Abstract
Rix 2004[573]	Incomplete reporting of outcome
Rucker 2009[590]	Less than minimum duration
Singh 2007[636]	Less than minimum duration
Tamez 2012[663]	No outcomes relevant to the protocol
Wesseling-perry 2011[717]	Not guideline condition
Wilkie 2009[719]	Intervention not in protocol (cinacalcet). Incorrect interventions
Xu 2012[728]	Abstract of systematic review

J.13 Oral bicarbonate supplements in the management of people with CKD and metabolic acidosis

Table 177: Studies excluded from the oral bicarbonate clinical review

Study	Exclusion reason
Abramowitz 2013[10]	Study focus is muscle strength - no relevant outcomes
Disthabanchong 2010[166]	Less than minimum duration
Goraya 2013[232]	Incorrect interventions. Comparison is not placebo or usual care
Susantitaphong 2012[659]	Systematic review: study designs inappropriate

Appendix K: Excluded economic studies

K.1 Self-management

Table 178: Studies excluded from the economic review

Reference	Reason for exclusion
Wei2010 [715]	No health benefits measured and a non-OECD population (Taiwanese) population. Costing study; it was selectively excluded in favour of cost utility analysis.

K.2 Blood pressure - combined renin-angiotensin-aldosterone system antagonists

Table 179: Studies excluded from the economic review (study highlighted in green from CG 73)

Reference	Title	Reason for exclusion
Studies identified in current CG73 (2008) clinical guideline		
[Burgess2004] [99]	Burgess ED, Carides GW, Gerth WC, Marentette MA, Chabot I, Canadian Hypertension Society. Losartan reduces the costs associated with nephropathy and end-stage renal disease from type 2 diabetes: Economic evaluation of the RENAAL study from a Canadian perspective. Canadian Journal of Cardiology 2004 May 1; 20(6):613-618	This economic evaluation is set in Canada and is based on data from the RENAAL trial. [Brenner2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the RENAAL trial. [Vora2005]
[Coyle2004] [142]	Coyle D, Rodby RA. Economic evaluation of the use of irbesartan and amlodipine in the treatment of diabetic nephropathy in patients with hypertension in Canada. Canadian Journal of Cardiology 2004 Jan; 20(1):71-79.	This economic evaluation is set in Canada and is based on data from the IDNT trial. [Lewis2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Palmer2004]
[Coyle2007] [141]	Coyle D, Rodby R, Soroka S, Levin A, Muirhead N, de Cotret PR, Chen R, Palmer A. Cost effectiveness of Ibesartan 300mg Given early versus late in patients with Hypertension and a history of Type 2 diabetes and renal Disease: A Canadian Perspective. Clinical therapeutics. 2007; 29(7):1508-1523	This economic evaluation is set in Canada and is based on data from the IDNT trial. [Lewis2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Palmer2004]
[Garattini1997] [219]	Garattini L, Brunetti M, Salvioni F, Barosi M.	This economic evaluation is set in

Reference	Title	Reason for exclusion
	Economic evaluation of ACE inhibitor treatment of nephropathy in patients with insulin-dependent diabetes mellitus in Italy. Pharmacoeconomics 1997 Jul; 12(1):67-75.	Italy and is based on data from the DNCSG trial. [Lewis1993] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Hendry1997]
[Herman2003] [265]	Herman WH, Shahinfar S, Carides GW, et al. Losartan reduces the costs associated with diabetic end-stage renal disease: the RENAAL study economic evaluation. Diabetes Care 2003 Mar;26(3):683-687	This economic evaluation is set in USA and is based on data from the RENAAL trial. [Brenner2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the RENAAL trial. [Vora2005]
[Palmer2006] [517]	Palmer AJ, Roze S, Valentine WJ, et al. Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland. Swiss Medical Weekly 2006 May 27;136(21-22):346-352.	This economic evaluation is set in Switzerland and is based on data from the IDNT trial. [Lewis2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Palmer2004]
[Palmer2003][519]	Palmer AJ, Annemans L, Roze S, Lamotte M, Rodby RA, Cordonnie DJ. An economic evaluation of irbesartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: cost-effectiveness of Irbesartan in Diabetic Nephropathy Trial (IDNT) in the Belgian and French settings. Nephrol Dial Transplant (2003) 18: 2059–2066	This economic evaluation is set in Belgium and France and is based on data from the IDNT trial. [Lewis2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Palmer2004]
[Rodby1996] [580]	Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. The Collaborative Study Group. Diabetes Care 1996 Oct;19(10):1051-1061	This economic evaluation is set in USA and is based on data from the DNCSG trial. [Lewis1993] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Hendry1997]
[Rodby2003] [579]	Rodby RA, Chiou CF, Borenstein J, et al. The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. Clinical Therapeutics 2003 Jul; 25(7):2102-2119.	This economic evaluation is set in USA and is based on data from the IDNT trial. [Lewis2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the IDNT trial. [Palmer2004]
[Stafylas2007] [647]	Stafylas PC, Sarafidis PA, Greka DM, Lasaridid AN. A cost-effectiveness analysis of	This economic evaluation is set in Greece. It has been excluded

Reference	Title	Reason for exclusion
	Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor blockers in Diabetic Nephropathy. The Journal of Clinical Hypertension. 2007; 9 (10):751-759	because it does not present an incremental analysis. It uses average 'numbers needed to treat' with ACE inhibitors and ARBs to estimate the average costs to prevent one patient developing ESRD.
[Souchet2003] [645]	Souchet T, Durand Z, I, Hannedouche T, et al. An economic evaluation of Losartan therapy in type 2 diabetic patients with nephropathy: an analysis of the RENAAL study adapted to France. Diabetes & Metabolism 2003 Feb; 29(1):29-35	This economic evaluation is set in France and is based on data from the RENAAL trial. [Brenner2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the RENAAL trial. [Vora2005]
[Szucs2004] [661]	Szucs TD, Sandoz MS, Keusch GW. The cost-effectiveness of losartan in type 2 diabetics with nephropathy in Switzerland--an analysis of the RENAAL study. Swiss Medical Weekly 2004 Aug 7;134(31-32):440-447	This economic evaluation is set in Switzerland and is based on data from the RENAAL trial. [Brenner2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the RENAAL trial. [Vora2005]
Studies identified in current clinical guideline update		
Adarkwah 2011 [13]	Cost-effectiveness of Angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in The Netherlands - A Markov model.	Strategies compared were not applicable to review question.
Citarella 2009[130]	Pharmacoeconomic consequences of losartan therapy in patients undergoing diabetic end-stage renal disease.	Abstract
De Portu 2011[157]	Economic consequences of losartan therapy in patients undergoing diabetic end stage renal disease in EU and USA.	This economic evaluation is set in France and is based on data from the RENAAL trial. [Brenner2001] It has been excluded because another study has been included which has a UK setting and which is also based on data from the RENAAL trial. [Vora2005]
Kutscherauer2009[362]	Cost-effectiveness analysis of add-on aliskiren to losartan treatment for patients with type 2 diabetes, hypertension and nephropathy in the Czech patients from payor perspective.	Abstract
Nevarez 2010[485]	Economic evaluation of aliskiren in type 2 diabetes and hypertension patients with nephropathy in Mexico	Abstract

Reference	Title	Reason for exclusion
Rudakova 2009 [591]	Pharmacoeconomics of direct renin inhibitor aliskiren in hypertension treatment of patients with type-2 diabetes and nephropathy.	Abstract

K.3 Vitamin D supplements in the management of CKD-mineral and bone disorders

Table 180: Studies excluded from the economic review

Reference	Reason for exclusion
Nuijten 2009 [492]	Selectively excluded. Setting- US perspective. The same study using a UK perspective was included.

Appendix L: Cost-effectiveness analysis: cystatin C testing in the diagnosis of CKD

L.1 Methods

L.1.1 Model overview

Estimated glomerular filtration rate (eGFR) is an estimate of kidney function routinely used in clinical practice because measuring GFR (mGFR) is impractical and costly. An eGFR of less than 60 mL/min/1.73m^2 on at least 2 occasions separated by >90 days defines Chronic Kidney Disease (CKD) stage 3 and below. Current practice in the UK is to estimate GFR from serum creatinine (SCr) using the isotope dilution mass spectrometry (IDMS) related MDRD (Modification of Diet in Renal Disease) equation.

The use of a marker of kidney damage (urinary albumin:creatinine Ratio, ACR) is also routinely used in clinical practice. The finding of an elevated urinary ACR (≥3 mg/mmol) defines CKD when the eGFR is ≥60 mL/min/1.73m^2 and refines the classification of CKD regardless of kidney function, providing prognostic information at any level of eGFR.

The use of a universal threshold eGFR of 60 mL/min/1.73m^2 for the diagnosis of CKD in the absence of markers of significant kidney damage has been a source of controversy since the international 5 stage classification of CKD was first introduced. This is partly driven by the increasing inaccuracy of the estimating equations at higher GFR levels. Derivation of a newer estimating equation based on the CKD Epidemiology Consortium creatinine equation (CKD-EPI$_{creat}$) equation, has improved the accuracy of estimated GFR. Measurement of an additional marker of kidney function, cystatin C, has also been suggested to better define CKD using the CKD-EPI cystatin C equation (CKD-EPI $_{cys}$), or a combined equation using creatinine and cystatin, the CKD-EPI $_{creat-cys}$. It is proposed that use of these

equations, particularly in the GFR range 45-59 mL/min/1.73 m^2, leads to more accurate diagnosis of CKD. Therefore the trade-offs are represented by the cost of the additional cystatin C measurements versus the cost of misdiagnosed patients (false positives) who are unnecessarily labelled as CKD and placed in a CKD management programme.

A significant number of patients will be affected by the choice of equation (~7% prevalence of CKD stages 3-5 in the general population using QICKD data). The guideline update literature review found no new evidence since the publication of CG73 on the cost-effectiveness of eGFR equations for this topic. As a consequence, the GDG has identified this topic as a high priority for an original economic analysis.

L.1.1.1 Comparators

Three diagnostic strategies for patients with suspected CKD (CKD-EPI_{creat} 45-59 and ACR <3) were devised to allow for differential use of diagnostic tests.

The strategies compared are:

- CKD-EPI_{creat}: In this strategy, no further testing is conducted and the person is diagnosed as having CKD stage 3a.
- CKD-EPI_{cys} : In this strategy, eGFR is re-calculated using serum cystatin C and the CKD-EPI_{cys} equation.
- CKD-$EPI_{creat-cys}$: In this strategy, eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation.

After reviewing the clinical evidence it was decided unnecessary to consider the MDRD equation since CKD-EPI_{creat} has both greater precision and less bias and is no more costly to administer.

L.1.1.2 Population

People with suspected CKD (CKD-EPI_{creat} eGFR 45-59 mL/min/1.73 m^2 and ACR <3), categorised into the following subgroups.

1) Adults 75+ years of age
2) Adults under 75 years of age
    - With and without hypertension

L.1.1.3 Time horizon, perspective, discount rates used

The time horizon was one year in the base case. The perspective was that of the UK NHS.

L.1.1.4 Outcomes

The main outcomes of the model are:

- Proportion of patients falsely diagnosed as having CKD (False positive - FP)
- Proportion of patients falsely diagnosed as not having CKD (False Negative - FN)
- NHS cost at 1 year

L.1.1.5 Deviations from NICE reference case

QALYs were not calculated. The GDG decided that the key outcome would be false positives avoided (not QALYs). This is because:

a) Most people, especially older people, who are eGFR 45-59 mL/min/1.73 m^2 will not progress to later stages of CKD

b) Although we use a GFR cut-off to diagnose CKD, kidney function is a continuum and therefore (before disease has progressed) the FP, TP, FN, FP will have (almost) identical quality of life.

c) It was felt that a substantial proportion of FNs would be picked up by re-screening before significant disease progression.

Given the main outcome selected by the GDG was the number of FPs avoided, it was felt that cost savings should be estimated over a short time horizon 12 months. This means that the cost savings associated with cystatin C are conservatively estimated. This was subjected to sensitivity analysis.

L.1.2 Approach to modelling

The model is a simple decision tree that categorises patients according to diagnostic outcomes (false positive (FP), true negative (TN), false negative (FN), and true positive (TP) results) – the model structure is presented in Figure 268.

L.1.3 Model inputs

Diagnostic accuracy data

The GDG requested data from studies in the guideline review for patients with CKD-EPI_{creat} 45-59 mL/min/1.73 m^2 and ACR<3mg/mmol. Data was sought from studies that contained both CKD-EPI_{creat} and CKD-EPI_{creat} . Data was received from the following studies:

- CKD-EPI derivation and validation cohorts[299].
    - Age<75 Hypertension, No diabetes (n=142)
    - Age>75 No hypertension, No diabetes (n=150)
- Kilbride et al (2013) [341,341]
    - Age 75+ (n=81)

Since there was little data for older patients, this was supplemented with unpublished data from the AGES-Reykjavik study[298], provided by the authors of the CKD-EPI study.

    - Age 75+ (n=156)

As indicated for the younger cohort we were able to sub-divide between those with and without hypertension and the few patients with diabetes were excluded. For the older cohort few patients did not have hypertension and a substantial proportion did have diabetes but the numbers were too small to allow further disaggregation.

The data is shown in Table 181. The individual results of the two 75+ cohorts are not presented because some of the data is academic in confidence. However, we can confirm that the prevalence, sensitivity and specificity across those two cohorts were very similar, suggesting that aggregation is not unreasonable.

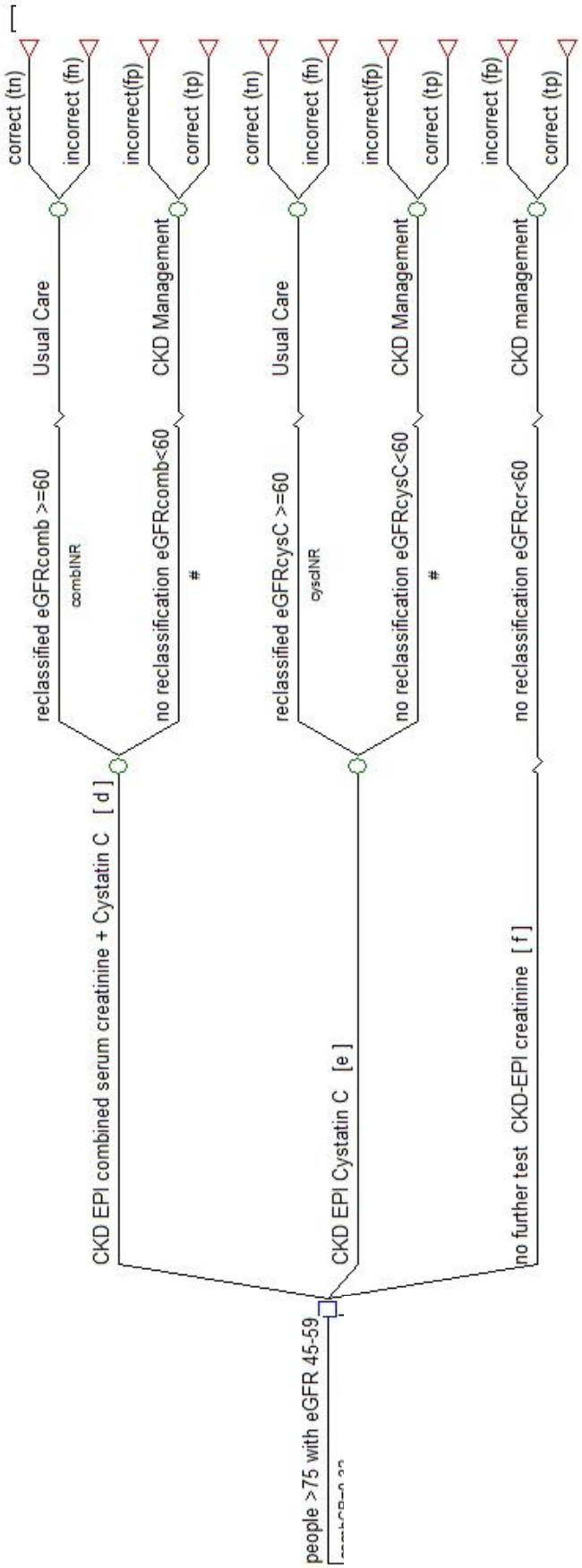


Figure 268: Decision Tree

Table 181 Diagnostic data

Age 75+

	CKD-EPI$_{cys}$			NO. of CD	CKD-EPI $_{creat-cys}$			NO. of CD
	mGFR<60	mGFR>60		183	mGFR<60	mGFR>60		192
TP	160	25	FP		TP	173	29	FP	
FN	29	23	TN		FN	16	19	TN	
Total	189	48	237		Total	189	48	237	

Age<75 No hypertension

	CKD-EPI $_{cysC}$			NO. of CD	CKD-EPI $_{creat-cys}$			NO. of CD
	mGFR<60	mGFR>60		113	mGFR<60	mGFR>60		121
TP	83	20	FP		TP	96	25	FP	
FN	17	30	TN		FN	4	25	TN	
Total	100	50	150		Total	100	50	150	

Age<75 Hypertension

CKD-EPI $_{cysC}$				NO. of CD
	mGFR<60	mGFR>60		112
TP	80	10	FP	
FN	20	32	TN	
Total	100	42	142	

CKD-EPI $_{creat-cys}$				NO. of CD
	mGFR<60	mGFR>60		112
TP	85	15	FP	
FN	15	27	TN	
Total	100	42	142	

CD=correct diagnoses, FN=false negative, FP=false positive, TN=true negative, TP=true positive.All mGFR values are measured in mL/min/1.73 m^2

Resource use and cost

Diagnosis

In the base case it was assumed that the cystatin C test is requested at the same time as the confirmatory creatinine test, 3 months after the first abnormal eGFR reading. Manpower, equipment and storage costs for the different strategies were considered equal and excluded from this analysis. In terms of resources required, the only difference between GFR estimation methods is the chemical reagent required for the laboratory analysis. Due to the lack of published information on the costs of diagnostic tests, the GDG estimated that the cost of a serum creatinine reagent was £0.25 and serum cystatin C reagent was £2.50.

In sensitivity analysis we looked at alternative scenario where the cystatin C test was ordered after the results of the confirmatory creatinine test are known. In this scenario there are no costs associated with the CKD-EPI$_{creat}$ strategy and for the other strategies we allocated the full cost of a serum creatine test assumed to be £3 plus another £3 for phlebotomy (SA3 and SA4).

Since there will be a number of false negative results from both cystatin C strategies, in a sensitivity analyses we added a re-test at 12 months including a test (£6) plus a 10 minute GP visit (£37) for patients who were classified as not having CKD (SA1 and SA4).

CKD management

The components of CKD management are described in Table 182. The unit costs of these components were taken from standard sources. Patients categorised as CKD-EPI_{cys} eGFR >60 mL/min/1.73 m^2 or CKD-$EPI_{creat-cys}$ eGFR >60 mL/min/1.73 m^2 do not incur these CKD management costs. They only accrue diagnostic test costs. No additional costs were assumed for false negative patients.

Drugs

It was hypothesised that people with CKD and hypertension might receive more intensive anti-hypertensive therapy. We conducted a comparison of antihypertensive costs for patients with (eGFR 45-59 mL/min/1.73 m^2) and without CKD (eGFR 60-89 mL/min/1.73 m^2) using data from general practice[329]- Table 183. The Drug and CKD management costs were estimated only for one year in the base case. However, in a sensitivity analysis, they were assumed to continue for 5 years (SA2). The annual cost of antihypertensive medication was lower by 15% (£7.00) in the group with eGFR 60-89 ml/min/1.73 m^2, which is probably an under-estimate since CKD patients might also be on higher doses of individual drugs.

Table 182: Annual Incremental cost of CKD management

Component	Unit Cost	Annual frequency	Source
GP visit 10 mins	£37.00	1	PSSRU 2012[146,146]
GP nurse visit 10 mins	£7.50	1	PSSRU 2012[146,146]
Biochemistry test	£3.00	1	NHS Reference Costs 2011-2012
Haematology test	£1.00	1	NHS Reference Costs 2011-2012
Phlebotomy	£3.00	1	NHS Reference Costs 2011-2012
Total cost	£51.50		

Table 183: Cost of antihypertensive medication

	Unit cost*	Patients with eGFR 45-59 ml/min/1.73 m^2 (n=7,993) [329]		Patients with eGFR 60-89 ml/min/1.73 m^2 (n=25,001) [329]		Assumption*	
Angiotensin-converting-enzyme inhibitor	£ 16.57	4884	61%	14263	57%	Weighted average of ramipril 10mg/day, lisinopril 20mg/day, perindopril erbumine 4mg/day	
Diuretic	£ 11.47	5056	63%	12374	49%	bendroflumethiazide	2.5 mg daily
Calcium channel blocker	£ 12.78	4271	53%	12410	50%	amlodipine	5 mg once daily
Beta blocker	£ 15.38	4032	50%	9787	39%	bisoprolol	10mg daily
Angiotensin receptor blocker	£ 40.71	2322	29%	6083	24%	Weighted average of irbesartan 150mg/day, candesartan 4mg/day, losartan 50mg/day	
Alpha blocker	£ 11.99	1391	17%	3551	14%	doxazosin	1 mg daily
Drugs per patient			2.15		2.34		
Weighted average cost			£ 46.10		£ 39.10		

** Source : National Drug Tariff 2012[486], Prescription Cost Analysis England 2012[487].*

L.1.4 Computations

Diagnostic Outcomes

For each equation patients were subdivided according to their estimated

	mGFR<60	mGFR>60
eGFR<60	True positive (TP)	False positive (FP)
eGFR>60	False negative (FN)	True negative (TN)

All GFR values units are ml/min/1.73 m^2

Using this data, we calculated the following:

Prevalence=$TP + FN / (FN + FP + TN + TP)$ [*Same for all equations]*

Specificity= $TN / (TN + FP)$

Sensitvity= $TP / (FN + TP)$

Diagnostic odds ratio (DOR)= $\frac{TP/FN}{FP/TN}$

For the probabilistic analysis we calculate

TP=Sensitvity x prevalence

FN=(1-sensitvity) x prevalence

TN=Specificity x (1-prevalence)

FN=(1-specificity) x (1-prevalence)

Where the specificity, prevalence and DOR are each defined by a distribution (see Uncertainty, below) and the sensitivity is defined as[660]:

Sensitvity= $1 \Big/ \left(1 + \frac{1}{DOR\left(\frac{1-specificity}{specificity}\right)}\right)$.

Costs

TP, FP=Test cost+drug cost+CKD management cost

TN, FN=Test cost only (+Re-test cost in sensitivity analysis)

L.1.5 Uncertainty

The base case model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter which was varied. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution. The model was run 10,000 times for the base case analyses and results were summarised.

We checked for convergence by plotting incremental cost on a graph for the probabilistic base case analysis. The incremental costs had converged by the 500th iteration.

The way in which distributions are defined reflects the nature of the data, so for example probabilties were given a beta distribution, which is bounded by zero and one, reflecting that a probability cannot be outside of this range. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 184: Description of the type and properties of distributions used in the probabilistic analysis

Parameter	Type of distribution	Properties of distribution
Prevalence of 'true' CKD Specificty Probability of being on a drug	Beta	Bounded between 0 and 1. Alpha=pN Beta=(1-p)N Where p=sample probability and N=sample size (For specificity N=the number of true neatives plus false positives in the sample)
Natural log of the diagnostic odds ratio (DOR)	normal	The DOR is bounded at zero. The mean of the distribution=ln(DOR). The standard error is defined as: $SEln(DOR) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$

Prices were left deterministic (that is, they were not varied in the probabilistic analysis). The sensitivity is calculated as a function of the DOR and the specificity, which captures the inverse relationship between sensitivity and specificity[224,660].

In addition sensitivity analyses were undertaken to test the robustness of model assumptions. These sensitivity analyses were conducted deterministically (that is, based on the parameter point estimates rather than their distributions). In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results.

Table 185: Prevalence and accuracy by cohort

	Prevalence	Sensitivity of eGFR CKD-EPI$_{cys}$	Specificity of eGFR CKD-EPI$_{cys}$	Sensitivity of eGFR CKD-EPI$_{creat-cys}$	Specificity of eGFR CKD-EPI$_{creat-cys}$
Age 75+	80%	85%	48%	92%	40%
Age<75 No hypertension	67%	83%	60%	96%	50%
Age<75 Hypertension	70%	80%	76%	85%	64%

Table 186: Base case results (probabilistic)

	Diagnostic outcomes			Mean costs (£)			
	Correct	FP	FN	Diagnosis	Additional drugs	CKD Care	Total
Age75+							
CKD-EPI$_{creat}$	79.8%	20.2%	0%	0.25		51.50	51.75
CKD-EPI$_{cys}$	76.6%	10.6%	12.9%	2.75		39.88	42.63
CKD-EPI$_{creat-cys}$	80.5%	12.2%	7.3%	2.75		43.60	46.35
Age<75 No hypertension							
CKD-EPI$_{creat}$	67%	33%	0%	0.25	0	51.50	51.75
CKD-EPI$_{cys}$	75%	13%	12%	2.75	0	35.36	38.11
CKD-EPI$_{creat-cys}$	81%	17%	3%	2.75	0	41.55	44.30
Age<75 Hypertension							
CKD-EPI$_{creat}$	70%	30%	0%	0.25	7.00	51.50	58.75
CKD-EPI$_{cys}$	79%	7%	14%	2.75	4.43	32.62	39.80
CKD-EPI$_{creat-cys}$	79%	11%	11%	2.75	4.93	36.29	43.97

FP=false positive, FN=false negative

Table 187: Base case results - incremental results (probabilistic)

	False Positives				False negatives				Cost (£)			
		Incremental vs CKD-EPIcreat				Incremental vs CKD-EPIcreat				Incremental vs CKD-EPIcreat		
	%		lower 95%	upper 95%	%		lower 95%	upper 95%	Mean		lower 95%	upper 95%
Age75+												
CKD-EPI$_{creat}$	20.2%				0.0%				51.75			
CKD-EPI$_{cys}$	10.6%	-9.7%	-13.8%	-6.3%	12.9%	12.9%	5.4%	24.4%	42.63	-9.12	-16.10	-4.05
CKD-EPI$_{creat-cys}$	12.2%	-8.0%	-11.8%	-4.9%	7.3%	7.3%	2.7%	15.7%	46.35	-5.40	-10.65	-1.80
Age<75 No hypertension												
CKD-EPI$_{creat}$	33.3%				0.0%				51.75			
CKD-EPI$_{cys}$	13.3%	-20.0%	-26.9%	-14.0%	12.1%	12.1%	4.9%	23.5%	38.11	-13.64	-17.60	-9.88
CKD-EPI$_{creat-cys}$	16.7%	-16.6%	-23.2%	-11.1%	2.7%	2.7%	0.7%	5.7%	44.30	-7.45	-10.99	-4.41
Age<75 Hypertension												
CKD-EPI$_{creat}$	29.6%				0.0%				58.75			
CKD-EPI$_{cys}$	7.0%	-22.5%	-29.6%	-16.1%	14.1%	14.1%	9.0%	20.2%	39.80	-18.94	-23.60	-14.39
CKD-EPI$_{creat-cys}$	10.6%	-19.0%	-25.7%	-13.0%	10.5%	10.5%	6.0%	16.0%	43.97	-14.77	-19.16	-10.56

Table 188: Sensitvity analysis (deterministic)

	Base case (probabilistic)	Base case (deterministic)	SA1	SA2	SA3	SA4
Age75+						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	42.63	42.95	52.39	203.75	46.20	55.64
CKD-EPI$_{creat-cys}$	46.35	46.64	52.99	222.22	49.89	56.24
Age<75 No hypertension						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	38.11	38.11	51.59	179.57	41.36	54.84
CKD-EPI$_{creat-cys}$	44.30	44.29	52.61	210.47	47.54	55.86
Age<75 Hypertension						
CKD-EPI$_{creat}$	58.75	58.75	58.75	292.74	58.50	58.50
CKD-EPI$_{cys}$	39.80	39.83	55.57	188.13	43.08	58.82
CKD-EPI$_{creat-cys}$	43.97	43.95	56.66	208.73	47.20	59.91

SA1=Sensitivity Analysis 1=The same as base case except that people that are CKD-EPI$_{cys}$>60 or CKD-EPI$_{creat-cys}$>60 are re-tested after 12 months incurring another test and a GP visit.

SA2=Sensitivity Analysis 2= The same as base case except that CKD drug and management costs are for 5 years (not 1 year)

SA3=Sensitivity analysis 3=The same as base case except that cystatin C test is ordered after the result of the follow-up creatinine test

SA4=Sensitivity analysis 4=The same as SA1 except that cystatin C test is ordered after the result of the follow-up creatinine test

L.2 Results

The prevalence of 'true CKD' (mGFR<60 ml/min/1.73 m^2) was lower in the younger cohorts suggesting that the CKD-EPI creatinine equation is over-predicting CKD in these patients (Table 185). Sensitivity of the test was similar across the 3 cohorts but specificity was greater in the younger cohorts particularly in the hypertensive cohort, suggesting that the CKD-EPI creatinine equation is over-predicting in younger people much more so than the two cystatin-based equations. Across all 3 cohorts the combined equation was more sensitive but the cystatin C equation was more specific.

In all 3 cohorts, the cystatin c equation produced the fewest false positive results, which led to it being the lowest cost strategy – the cost of the test being more than offset by the subsequent reduction in drug and management costs (Table 186 and Table 187). In the cohort of older patients and the cohort of non-hypertensive patients, it was actually the combined equation that had the most accurate diagnoses since it had fewer false negative results due to its greater sensitivity.

If we consider CKD management costs over 5 years then the cost savings per patient tested compared with the creatinine test alone increase (Table 188) – for example, for younger patients without hypertension they increased from £14 to £78 per patient.

If we add the cost of a follow-up test (Table 188) to try and pick up false negatives after a year then CKD-EPI_{cys} is the least cost strategy for younger patients but not for older patients. However, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the lowest cost strategy for older patients as well.

If the cystatin C test is ordered after the results of the follow-up test are known (Table 188) then the CKD-EPI_{cys} is the least cost strategy but not if there is a follow-up test to try and pick up false negatives after a year. However, again, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the lowest cost strategy again.

L.3 Interpreting Results

L.3.1 Summary of results

Additional eGFR measurement for people with CKD-EPI_{creat} eGFR 45-59 ml/min/1.73 m^2 is cost saving and reduces the number of false positives compared to eGFR measurement with serum creatinine alone for all subgroups investigated. However, additional GFR estimation using cystatin C or cystatin C + creatinine for people with CKD-EPI_{creat} eGFR 45-59 ml/min/1.73 m^2 will also increase the number of false negatives identified.

L.3.2 Limitations and Interpretation

The GDG considered False Positives as the outcome of greatest concern because of the risks of medication and the unnecessary anxiety caused by over-diagnosis, which may have broader impacts on patients including life insurance premiums. The GDG assumed that False Negatives would not experience significant adverse effects as they would mostly be identified in the future according to other symptoms.

It would be difficult to estimate the longer-term cost and health impact of the different strategies, since this would depend on the progression of disease in the CKD negative patients (CKD-EPi$_{creat}$ 45-59 and CKD-EPI$_{creat\ cys}$=60+ and ACR,3) and how that progression is affected by CKD management, which we believe is not known with any precision. But it is acknowledged that this is a limitation of the analysis. However, it is perhaps not a serious one since most false negatives would be subsequently identified before significant progression especially if there is re-testing of CKD-negative patients after 12 months, as in the sensitivity analysis. The analysis was assessed as partially applicable since it did not estimate quality-adjusted life-years.

The cost savings attributable to cystatin c testing were sensitive to some of the assumptions made. For example the addition of the cost of a re-test after 12 months to pick up patients previously given a false negative result meant that there were not net savings. But even in this scenario, when the conservative time horizon of 1 year was increased to 2 years then savings were apparent again. This means that re-testing at 1 year might be the optimal strategy. In the absence of re-testing at 1 year, the use of the CKD-EPI$_{creat-cys}$ equation could be considered a reasonable option being the most accurate test and with much of the cost savings of the CKD-EPI$_{cys}$ equation strategy. The analysis cannot definitively conclude which is more cost-effective CKD-EPI$_{creat-cys}$ or CKD-EPI$_{cys}$ since there is a trade-off between accuracy and cost.

The guideline's clinical review did not reveal strong evidence for differences in the relative accuracy of the different equations according to ethnicity or the presence of cardiovascular disease or diabetes or a history of acute kidney injury and therefore the findings of this analysis are likely to apply to all these subgroups. The cost savings we observed are only for people without diabetes. For those with diabetes, unless stage of CKD has significantly progressed, CKD management is unlikely to add to their NHS costs, since they will already be having regular contact with primary care and regular testing of kidney function. However, the GDG felt that a separate diagnostic testing strategy for patients with diabetes would be confusing and therefore a single recommendation was made for all the comorbidity subgroups.

L.3.3 Evidence statement

One original comparative cost analysis found that CKD-EPI$_{cys}$ was less costly than CKD-EPI$_{creat}$ and CKD-EPI$_{creat-cys}$ for diagnosing CKD in people with CKD-EPI$_{creat}$45-59, ACR<3mg/mmol and without diabetes (magnitude of cost savings varied according to age group, comorbidity, time horizon and re-testing strategy). This analysis was assessed as partially applicable with minor limitations.

Appendix M: Cost-effectiveness analysis: Novel oral anticoagulants for people with CKD and non-valvular atrial fibrillation

M.1 Methods

M.1.1 Model overview

The model evaluates the cost-effectiveness of apixaban or dabigatran compared with warfarin and aspirin based on the results of CKD subgroups from the ARISTOTLE[275] and AVERROES[180] and RE-LY[266] trials.

Population

People with both chronic kidney disease and non-valvular atrial fibrillation.

The trials subgrouped together patients with an eGFR below 50. Those with an eGFR below 25 were excluded from the trials.

Comparators

For this population (CKD and non-valvular atrial fibrillation) there was clinical effectiveness evidence for apixaban, dabigatran, rivaroxaban, aspirin and warfarin (see 10.3.3).

The evidence for **apixaban** showed survival benefit in the CKD subgroup as well as a reduction in stroke and systemic embolism and major bleeding compared with both warfarin and aspirin.

The evidence for **dabigatran** showed no survival benefit in the CKD subgroup although there was a reduction in stroke and systemic embolism.

The evidence for **rivaroxaban** was very low and low quality and did not demonstrate clearly clinical effectiveness:

- there was no clinically effective difference between 15mg rivaroxaban and warfarin in terms of reducing risk of ischemic stroke or haemoglobin drop, transfusion, clinical organ or fatal bleeding;
- the evidence suggested that rivaroxaban may be more effective in terms of reducing haemorrhagic stroke, undetermined stroke and intracranial haemorrhage, but there was uncertainty in the magnitude and direction of this effect.

Therefore only aspirin, warfarin and apixaban were included as comparators in the base case analysis. Dabigatran was considered only in a sensitivity analysis because of the lack of evidence of a

survival benefit. Rivaroxaban was not included because of the general lack of evidence of effectiveness.

Time horizon, perspective, discount rates used

A lifetime horizon was taken.

The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.

M.1.2 Approach to modelling

Model structure

A simple life-table was constructed to estimate life expectancy (discounted and undiscounted) for each cohort (apixaban, aspirin and warfarin).

Key assumptions

- The hazard ratios from the trials were extrapolated to the lifetime horizon
- In each cohort the rates of major bleeding and stroke or systemic embolism from the trial were assumed to be constant over the lifetime.
- The difference in QALYs was derived chiefly from the difference in survival; quality of life was assumed to be the same, except that a disutility was applied to each episode of stroke or systemic embolism
- Costs included were:
    - drugs
    - anticoagulation clinic visits (warfarin)
    - treatment of major bleeding
    - treatment of stroke or systemic embolism
    - other CKD treatment

Uncertainty

The base case model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter which was varied. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 10,000 times for the base case analyses and results were summarised.

We checked for convergence by plotting summary estimates of cost-effectiveness (incremental net monetary benefit, INMB) on a graph for the probabilistic base case analysis. The INMB for apixaban vs warfarin had converged by the 500th iteration but the INMB for apixaban vs aspirin was only stable

by the 5000th iteration, reflecting the wider confidence intervals for the treatment effects for this comparision.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by zero and one, reflecting that a mean utility will not be outside this range. Probability distributions in the analysis were parameterised using error estimates from data sources. Where this was not possible assumptions were made.

Table 189: Description of the type and properties of distributions used in the probabilistic analysis

Parameter	Type of distribution	Properties of distribution
Treatment effects (natural log of hazard ratio)	Normal	The mean of the distribution was calculated as follows: Mean = ln(HR) – $(SE)^2/2$ The standard error (SE) of the natural log of the hazard raio was calculated by: SE = [ln(HRupper CI) – ln(HRlower CI)]/1.96*2
Utility	Beta	Bounded between 0 and 1. Derived from mean utility and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2*((1-mean)/SE^2)-mean$ Beta = Alpha*((1−mean)/mean)
Baseline rates Disutility associated with a stroke or systemic embolism Treatment costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = SE^2/Mean Where the standard error was unknown it was assumed that SE = mean/4 (as in TA275)

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis): the cost-effectiveness threshold (which was deemed to be fixed by NICE), drug prices and the mean age and sex distribution of the cohort.

In addition sensitivity analyses were undertaken to test the robustness of model assumptions. These sensitivity analyses were conducted deterministically (that is, based on the parameter point estimates rather than their distributions). In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results.

M.1.3 Model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data from the economic models of the Apixaban NICE Technology Appraisal (TA275) and the NICE CKD clinical guideline (CG73)[471].

Initial cohort settings and baseline event rates were taken from the ARISTOTLE trial. Treatment effects were taken from both the ARISTOTLE and AVERROES trials (and for the dabigatran sensitivity analysis, the RE-LY trial).

Initial cohort settings

The ARISTOTLE trial[275] did not report the age/sex distribution for the CKD-EPI$_{creat}$<50 ml/min/1.73m^2 cohort. Instead we used a mean age of 75 and 46% female, as these were the averages of the two other CKD cohorts defined in the trial (Table 190).

Table 190: Patient characteristics reported for ARISTOTLE CKD cohorts

	Cockroft-Gault ≤50ml/min/1.73m^2	Cystatin C estimated GFR ≤50ml/min/1.73m^2
Mean age	77.6	73.3
Female sex	53.3%	38.0%

The CKD cohort of the AVERRORES trial[180] had a similar age-sex distribution: mean age 75 and 49% female.

Baseline event rates (event rates for patients on warfarin)

The baseline rates for major bleeding and stroke or systemic embolism were taken from the warfarin arm of the ARISTOTLE trial[275] (Table 191).

Table 191: Outcomes from trials (baseline rates per year and hazard ratios)

	Warfarin(a)	Hazard ratio - apixaban vs.warfarin(95 %CI)(a)	Hazard ratio - apixaban vs.aspirin(95 %CI)(b)	Hazard ratio - dabigatran 110mg vs.warfarin(95%CI)(c)	Hazard ratio - dabigatran 150mg vs.warfarin(95%CI)(c)
Death (all cause)	7.5%	0.78 (0.63, 0.96)	0.86 (0.61, 1.2)	0.97 (0.77, 1.24)	1.03 (0.82, 1.30)
Major bleeding	6.8%	0.48 (0.37, 0.64)	1.2 (0.65, 2.1)	1.02 (0.78, 1.33)	1.22 (0.95, 1.58)
Stroke or systemic embolism	2.1%	0.61 (0.39, 0.94)	0.32 (0.18, 0.55)	0.78 (0.51, 1.21)	0.55 (0.34, 0.89)

(a) The eGFR <50 ml/min/1.73m^2 (CKD-EPI$_{creat}$) cohort (n=2843) of the ARISTOTLE trial
(b) The eGFR <50 m/min/1.73m^2 (Cockcroft-Gault) cohort (n=1697) of the AVERROES trial
(c) The eGFR <50 m/min/1.73m^2 (CKD-EPI$_{creat}$) cohort (n=3374) of the RE-LY trial

For mortality we estimated a mortality ratio and applied it to the mortality rates for a cohort from the general population with a starting age of 75. We estimated the mortality ratio as follows:

1. We extracted the mortality rates for males and females age 75 for the England and Wales general population (source: ONS)

2. We estimated a weighted average of the two figures assuming 46% female: 2.9%
3. We divided the mortality rate from the warfarin cohort (Table 191) by the mortality from the England and Wales cohort: 7.5%/2.9%=2.6

We then multiplied this ratio with the age-specific mortality rates for England and Wales to get our baseline age-specific mortality for our life-table (Table 192).

Table 192: Baseline age-specific mortality

Age	Gen popn	Model cohort (warfarin)
75	0.029	0.075
76	0.033	0.085
77	0.037	0.094
78	0.041	0.106
79	0.046	0.119
80	0.053	0.135
81	0.059	0.151
82	0.067	0.171
83	0.075	0.192
84	0.085	0.216
85	0.095	0.243
86	0.106	0.271
87	0.120	0.307
88	0.134	0.344
89	0.154	0.394
90	0.165	0.422
91	0.178	0.457
92	0.193	0.494
93	0.221	0.567
94	0.250	0.639
95	0.275	0.704
96	0.298	0.764
97	0.324	0.830
98	0.351	0.899
99	0.372	0.952
100	0.399	1.022

Relative treatment effects (apixaban vs.warfarin)

In the base case analysis we used for the relative treatment effects, the hazard ratios reported for the eGFR <50 ml/min/1.73m^2 (CKD-EPI$_{creat}$) cohort of the ARISTOTLE trial[275] (Table 191).

However, the ARISTOTLE trial authors note that the treatment effects for mortality were quite different depending on how CKD is defined (see their Figure 1); when defining CKD using cystatin C they found no treatment effect at all for apixaban over warfarin (HR=1.0). They conclude that 'the findings in patients with different degrees of renal function are consistent with the results of the overall trial'. Therefore in a sensitivity analysis (SA1) we use the treatment effect for the overall trial cohort (hazard ratio=0.89), which is a more modest treatment effect than the base case (hazard ratio=0.78).

Relative treatment effects (apixaban vs.aspirin)

In the base case analysis we used for the relative treatment effects, the hazard ratios reported for the eGFR <50 ml/min/1.73m^2 cohort of the AVERROES trial[180] (Table 191).

In a sensitivity analysis (SA1) we use the treatment effect for the overall trial cohort (hazard ratio=0.79), which is a bigger treatment effect than the base case (hazard ratio=0.86).

Relative treatment effects (dabigatran vs.warfarin)

In a sensitivity analysis we used for the relative treatment effects, the hazard ratios reported for the eGFR <50 ml/min/1.73m^2 cohort of the RE-LY trial[266] (Table 191).Utilities

Utilities indicate health-related quality of life on a scale where 0 equates to no better than being dead and 1 is equal to full health. The NICE chronic kidney disease guideline model (CG73) used an estimate of 0.73 for CKD stage 3/4 and 0.60 for CKD Stage 5. For the apixaban model we used the higher estimate in the base case analysis and lower one, in a sensitivity analysis (SA2).

For a stroke / ststemic embolism event we used a utility of 0.675, taken from the NICE technology appraisal on apixaban for non-valvular atrial fibrillation (TA275). We multiplied this figure with the CKD utility to give a figure of 0.52 in the base case or put another way a disutility of 0.23.

A disutility was not applied to bleeding events.

Costs

Unit costs for CKD care were taken from the NICE CKD clinical guideline model (CG73) - Table 193. These costs included inpatient stays, nephrology outpatient visits, antihypertensive drugs and GP visits. The costs were inflated from 2006-7 prices to 2011-12 prices using the Hospital & Community Health Services Pay and Prices Index[146].

Anticoagulation, bleeding and stroke / systemic embolism costs were taken from the model of the NICE technology appraisal on apixaban for non-valvular atrial fibrillation (TA275). In sensitivity analyses we use more conservative estimates for CKD care cost (SA3) and stroke / systemic embolism event costs (SA4).

Table 193: Unit costs

	Base case	Notes	Source
Cost per year			

	Base case	Notes	Source
Apixaban/dabigatran	802		TA275
Aspirin	26		TA275
Warfarin	44		TA275
Anticoagulation clinic	248		TA275
CKD care	3281	CKD Stage 3/4	CG73
CKD care – SA3	5119	CKD Stage 5	CG73
Cost per episode			
Major bleeding	1493	Weighted average of GI bleed admissions	TA275
Stroke or systemic embolism	4078	Acute care for systemic embolism	TA275
Stroke or systemic embolism – SA4	1658	Acute care for systemic embolism – conservative estimate	TA275

M.1.4 Computations

The model was constructed in Microsoft Excel and was evaluated by life table analysis.

Mortality rates were converted into probabilities using the following formulae:

$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where r = selected rate t= cycle length (months)

For each year of the life table the life-years (LYs) are the average of the number of patients alive at the beginning of the year and the number alive at the end. The number of patients alive was discounted to reflect time preference (discount rate = 3.5%) using the following formula:

$\text{Discounted total} = \frac{\text{Patients Alive}}{(1+r)^n}$	Where: r = discount rate per annum=3.5% n = time (years)

The discounted life-years were then summed across all the years of the life-table.

The (discounted) number of bleeding events for each treatment was the respective bleeding rate (see Table 191) multiplied by the number of (discounted) life-years. The number of episodes of stroke or systemic embolism was calculated in the same manner.

Discounted QALYs were estimated by multiplying the CKD utility with the number of discounted life-years and then subtracting the discounted number of stroke / systemic embolism events multiplied by the stroke / systemic embolism dis-utility (see Utilities, above).

Discounted costs were the discounted life-years multiplied by the anticoagulation and CKD treatment costs plus the discounted number of stroke / systemic embolism and bleeding events each multiplied by the episode cost (See Table 193).

M.1.5 Model validation

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs.

M.1.6 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs/QALYs(X) = total costs/QALYs for option X	• Cost-effective if: ICER < Threshold

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

M.2 Results

M.2.1 Base case

Of the three treatments, aspirin had the fewest major bleeding events but apixaban had the fewest stroke or systemic embolism events and the best survival with a gain of 0.62 QALYs compared with warfarin and 0.44 QALYs compared with aspirin (Table 194).

The incremental costs of apixaban were augmented by the cost of CKD care in additional months of life and only partially offset by the avoidance of INR monitoring and reduced events. The cost per QALY gained was £9,748 compared with aspirin and £14,637 compared with aspirin, indicating that apixaban is cost-effective for patients with CKD and non-valvular atrial fibrillation.

With a threshold of £20,000 per QALY gained, apixaban was ranked first in 62% of simulations, aspirin in 34% and warfarin in only 4% (Table 195).

The analysis was assessed to have direct applicability and only minor limitations.

M.2.2 Sensitivity analyses

In the most conservative analysis, apixaban was slightly over the £20,000 per QALY threshold compared with warfarin (Table 196) at £20,840. In all other analyses, apixaban was cost-effective compared with warfarin. The results were most sensitive to the mortality treatment effect.

Likewise in the most conservative analysis, apixaban was slightly over the £20,000 per QALY threshold compared with aspirin (Table 196) at £22,598. In all other analyses, apixaban was cost-effective compared with aspirin. The results were most sensitive to the CKD utility.

For dabigatran 110mg the reduction in stroke or systemic embolism and very small gain in survival was not cost effective even at a threshold of £30,000 per QALY (it cost £43,700 per QALY gained). For dabigatran 150mg the very small increase in mortality and the increase in major bleeding meant that there were actually QALYs lost compared with warfarin.

Table 194: Base case results (probabilistic)

	Apixaban	Warfarin	Aspirin		Apixaban vs Warfarin				Apixaban vs Aspirin		
Mean health outcomes (undiscounted)						L95%	U95%			L95%	U95%
Major bleeding events	0.27	0.48	0.22		-0.21	-0.30	-0.12		0.05	-0.13	0.17
Stroke / systemic embolism events	0.11	0.15	0.33		-0.04	-0.09	0.01		-0.22	-0.53	-0.06
Life years	8.23	7.07	7.49		1.16	0.17	2.19		0.74	-0.85	2.19
Mean health outcomes (discounted)											
Major bleeding events	0.22	0.41	0.19		-0.18	-0.25	-0.11		0.04	-0.11	0.14
Stroke / systemic embolism events	0.09	0.13	0.28		-0.04	-0.08	0.01		-0.19	-0.44	-0.05
Life years	6.83	6.00	6.30		0.84	0.12	1.56		0.54	-0.59	1.61
QALYs	***4.97***	***4.35***	***4.53***		***0.62***	***0.10***	***1.14***		***0.44***	***-0.38***	***1.21***
Mean costs (£, discounted)											
Drugs	5,481	263	161		5,218	4,551	5,911		5,320	4,666	6,003
Anticoagulation clinic	-	1,491	-		- 1,491	- 2,324	- 849		-	-	-
Annual CKD care	22,436	19,695	20,674		2,741	375	5,919		1,761	- 1,958	5,854
Major bleeding events	336	609	282		- 273	- 475	- 126		53	- 168	224
Stroke / systemic embolism events	363	521	1,124		- 159	- 372	27		- 762	- 1,958	- 176
Total	***28,615***	***22,580***	***22,242***		***6,035***	***2,925***	***9,785***		***6,373***	***582***	***11,904***
Cost per QALY gained (£, discounted)					***9,748***	P(20k)	0.95		***14,637***	P(20k)	0.66
						p(30k)	0.98			p(30k)	0.75

Table 195: Ranking of strategies at a threshold of £20,000 per QALY gained (proportion of simulations)

Rank	Apixaban	Warfarin	Aspirin
1	62%	4%	34%
2	36%	27%	37%
3	2%	69%	29%

Table 196: Deterministic sensitivity analyses

	Apixaban vs Warfarin				Apixaban vs Aspirin		
	Incremental cost (£)	QALYs gained	Cost per QALY gained (£)		Incremental cost (£)	QALYs gained	Cost per QALY gained (£)
Base case (probabilistic)	6,035	0.62	9,748		6,373	0.44	14,637
Base case (deterministic)	5,949	0.60	9,855		6,324	0.40	15,687
SA1: mortality effect from whole trial population	4,110	0.28	14,460		6,902	0.58	11,912
SA2: Lower CKD utility	5,949	0.50	11,951		6,324	0.34	18,692
SA3: higher CKD cost	7,445	0.60	12,333		7,239	0.40	17,959
SA4: Lower Stroke / systemic embolism event cost	6,043	0.60	10,012		6,729	0.40	16,694
SA5:Worst case scenario	4,907	0.24	20,840		7,645	0.34	22,598
	Dabigatran vs Warfarin						
SA6: Dabigatran 110mg vs Warfarin	3,366	0.08	43,729				
SA7: Dabigatran 150mg vs Warfarin	2,558	-0.05	Ineffective				

Appendix N: Research recommendations

N.1 Low-dose aspirin in preventing cardiovascular disease

Research question: For people with CKD at the highest risk of cardiovascular disease, what is the clinical effectiveness of low-dose aspirin compared with placebo for primary prevention of cardiovascular disease?

Why this is important: CKD is a common long-term condition and a powerful independent predictor of cardiovascular disease. The risks are increased as the estimated glomerular filtration rate (eGFR) decreases and level of albuminuria increases. Kidney Disease: Improving Global Outcomes (KDIGO) classifies people with CKD as being at moderate risk, high risk or very high risk of cardiovascular disease according to their eGFR and albumin:creatinine ratio (ACR). However, the current evidence base for reducing cardiovascular risk in the CKD population is very limited.

Table 197: Criteria for selecting high-priority research recommendations

PICO question	In people in people with CKD at high-risk and very-high risk of cardiovascular disease and end stage renal disease (as defined by the KDIGO 2012 classification of CKD) but without a history of pre-existing cardiovascular disease (primary prevention), what is the effect of low-dose aspirin compared with placebo in reducing cardiovascular events, mortality and improving health related quality of life and at what cost in terms of major bleeding?
Importance to patients or the population	A substantial body of evidence supports the use of aspirin in the secondary prevention of cardiovascular disease, but the data for primary prevention is conflicting. The evidence that CKD is a powerful risk factor for cardiovascular disease is incontrovertible. We know the risks are increased further at all categories of eGFR by the presence of albuminuria. However despite this wealth of epidemiological data we have very limited evidence on how to modify the risks. The absolute benefits of aspirin may be greater in a high-risk CKD population,

	but the risks of haemorrhagic complications may also be higher, especially where the eGFR is significantly reduced. Conversely people with albuminuria and a preserved eGFR may be subject to greater benefit from antiplatelet agents as compared with the general population but without an increased risk of bleeding. Establishing this balance between the risks and benefits is therefore of critical importance to very large number of patients.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use of antiplatelet agents as primary prevention in people with CKD at high and very high risk of adverse outcomes.
Relevance to the NHS	CKD is a highly prevalent condition, affecting up to 13% of the population (all stages). The Kidney Disease Improving Global Outcomes (KDIGO) 2012 classification of CKD categorises people with CKD as being at moderate risk, high risk, or very high risk of cardiovascular disease and end-stage renal disease according to the level of both eGFR and ACR. It is estimated that almost 4% of the population are in the high-risk and very high-risk categories (eGFR<45ml/min/1.73m^2; eGFR<60ml/min/1.73m^2 and ACR>3mg/mmol; eGFR>60ml/min/1.73m^2 and ACR>30mg/mmol). Epidemiological data suggest that approximately 80% of those with an eGFR<60ml/min/1.73m^2 do not have a history of pre-existing cardiovascular disease, falling to 50% in those with an eGFR<30ml/min/1.73m^2. Establishing evidence for the primary prevention of cardiovascular disease is therefore of relevance to large number of patients. Aspirin is an inexpensive therapy with the potential to reduce amenable morbidity and mortality and increase amenable quality of life in people with CKD, whilst reducing healthcare costs.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework. The Department of Health Cardiovascular Outcomes Strategy seeks to improve

	outcomes in people with or at risk of cardiovascular disease, and highlights the need to manage cardiovascular disease as a single family.
Current evidence base	The current evidence is considered in chapter 10.2.3. When used for secondary prevention aspirin reduces the risk of major cardiovascular events in the general population by 15 events per 1,000 patient-years. In primary prevention 0.6 events per 1,000 patient-years are prevented, but at the expense of 0.3 major bleeding events per 1,000 patient-years. Data in CKD is limited but suggestive of a benefit. In a subgroup analysis of the HOT trial, in people with an eGFR of 45-59ml/min/1.73m^2, 8 (-7 to 22) major cardiovascular events were prevented per 1,000 patient years with 4 (-2 to 10) major bleeds per 1,000 patient years; for those with an eGFR<45ml/min/1.73m^2, 76 (31 to 121) events were prevented at a cost of 39 (5 to 72) bleeds. There was evidence of significant heterogeneity by eGFR. However this was a post-hoc analysis, only 2.9% of the population had an eGFR<45ml/min/1.73m^2, reporting of bleeding episodes was imprecise, and no data was provided on proteinuria.
Equality	CKD is particularly prevalent in older people, and the study design should recognise this.
Study design	A randomised double-blind placebo-controlled trial is required to address this question. Patients will ideally be recruited from primary care, as this is where most people with CKD are treated. Our recommendation is that people in the high risk and very high risk groups without a prior history of cardiovascular disease are included. Better evidence on how to measure risk in CKD may allow the inclusion criteria to be refined. The intervention is low dose (75mg) aspirin or placebo. For patients at increased risk of bleeding (e.g. eGFR<45ml/min/1.73m^2), consideration should be given to testing whether the administration of concomitant gastro-protection reduces the risks of bleeding. The end-points should include: major cardiovascular events (composite);

	myocardial infarction; stroke; cardiovascular mortality; all-cause mortality; hospitalisation; health-related quality of life; major and minor bleeding. Subgroups should include people with diabetes, older people, and CKD stages.
Feasibility	CKD is highly prevalent, and the quality of general practice data in the UK, including albuminuria recording, is relatively high. Patients with CKD and albuminuria are likely to experience relatively high event rates. There should be no particular ethical or technical issues.
Other comments	The trial is most unlikely to attract commercial sponsors. However, given the size of the problem, the potential impact to patients and the NHS, and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding.
Importance	This study is of high importance.

N.2 Self-management

Research question: Does the provision of educational and supportive interventions to people with CKD by healthcare professionals increase patients' skills and confidence in managing their conditions and improve clinical outcomes?

Why this is important: CKD is a common long-term condition that frequently co-exists with other long-term conditions, including diabetes, cardiovascular disease and depression, and is associated with reduced quality of life. Through greater understanding of their conditions and provision of the information needed to support lifestyle change, people with CKD may be better able to live well with their long-term condition(s). Self-management may also improve their biomedical markers, for example, blood pressure.

People with earlier stage CKD (not considered here) may benefit from a similar approach to self-management to one which might be adopted in people with hypertension, diabetes and cardiovascular disease.

People with advanced CKD may benefit from education and support on particular issues, such as preparation for renal replacement, symptom management and specific dietary modifications. However, the current evidence base for self-management support in the CKD population is very limited.

Table 198: Criteria for selecting high-priority research recommendations

PICO question	In people with CKD stage 4 does the provision of educational and supportive interventions by healthcare professionals increase patients' skills and confidence in managing their conditions and improve outcomes (HRQOL, unplanned starts on renal replacement, hospitalisation, and achievement of biomedical targets) as compared to general (non-multidisciplinary) renal care? The interventions should include: health information and patient education; telephone support and access to a support group; and electronic support, which could be based on the Renal Patient View system (see study design, below, for references to examples of interventions). The control group will receive usual general (non-multidisciplinary) renal care (including blood pressure control and cardiovascular risk reduction, and treatment where present of renal anaemia and CKD mineral bone disorder).
Importance to patients or the population	CKD is a common long-term condition that frequently co-exists with other long-term conditions, particularly diabetes, cardiovascular disease and depression, and is associated with reduced quality of life. The more advanced stages are less common but CKD stage 4 still affects approximately 0.4% of the adult population. We need to know how best to support patients to take control of their conditions, in order to improve outcomes that matter to them.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use the use of self-management support systems in people with CKD.
Relevance to the NHS	A substantial proportion (up to 2%) of the NHS budget is spent to treating disease. Helping people to help themselves is therefore of great relevance to the health service.
National priorities	This question is of central relevance to Domain 2 of the NHS Outcomes

	Framework "Helping people to live well with a long-term condition". It could also impacts upon Domains 1 and 4.
Current evidence base	Quality of life is significantly impaired in people with CKD. For patients with advanced or progressive disease, unplanned starts on renal replacement are associated with worse clinical outcomes and greater costs. Both of these elements might be improved with a greater involvement of patients in their own care. However the evidence base for self-management in CKD is extremely limited.
Equality	CKD is particularly prevalent in older people and black and minority ethnic groups, and the study design should recognise this. It is also important that the research consider those with poor health literacy, low socio-economic status and address accessibility issues to self-management systems.
Study design	This question would be best answered with an individual patient level randomised control trial, or series of trials. The suggested study population is people with 4 CKD who are anticipated to be more than 1 year from requiring renal replacement The intervention would need to be carefully considered, and defining this should include the involvement of expert patients, but might include elements of: • Provision of health information (could include access to Renal Patient View-type system) • Education (both disease-specific and transferrable self-management skills) • One-to-one support • Group support. Examples include: Chen SH, Tsai YF, Sun CY, Wu IW, Lee CC, Wu MS. The impact of self-management support on the progression of chronic kidney disease. A

	prospective randomized controlled trial. Nephrol Dial Transplant. 2011 Nov;26(11):3560-6), and: Ong SW, Jassal SV, Porter E, Logan AG, Miller JA. Using an electronic self-management tool to support patients with chronic kidney disease (CKD): a CKD clinic self-care model. Semin Dial. 2013 Mar-Apr;26(2):195-202), which could include elements of the well-established Renal Patient View IT system (https://www.patientview.org/). A matched control group should receive no intervention. The end-points should include: • Measures of patient activation • Quality of life • Symptom burden • Unplanned starts on dialysis (Indicator for Quality Improvement LT13) • Hospitalisation And could include: • Biomedical measures, e.g. phosphate, haemoglobin • Progression of renal disease. Preliminary work will be required to determine how to best measure patient activation and quality of life in this patient group. Subgroups should include older people, BME groups and diabetes
Feasibility	Yes – significant numbers of people have CKD 4, and would most easily be recruited from secondary care. Preliminary work will be required to determine how to best measure patient activation and quality of life in this patient group. There should be no particular ethical or technical issues.
Other comments	Unlikely to be commercially funded.
Importance	This study is of high importance.

N.3 Vitamin D supplements in people with hyperparathyroidism secondary to CKD

Research question: In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes?

Why this is important: Further research is needed to identify if use of vitamin D or vitamin D analogues improve outcomes in patients with CKD. Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function declines. Abnormalities of circulating hormone concentrations related to CKD mineral and bone disorder (CKD-MBD) include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D). At the tissue level there is down regulation of vitamin D receptors and resistance to the actions of PTH. The prevalence of hyperparathyroidism increases from 5.5% in those with a GFR>90 ml/min/1.73m^2 to 23%, 44% and 73% in people with GFRs 45-59, 30-44 and <30 ml/min/1.73m^2 respectively. 25-Hydroxyvitamin D deficiency is twice as prevalent in people with a GFR <30 ml/min/1.73m^2 compared with those with normal GFR[297,381311,396310,394309,393308,392308,392307,391302,382]. Decreased bone mass and changes in bone microarchitecture occur and progress early in CKD such that patients with CKD increasing the risk of bone fracture. Replacing vitamin D in people with CKD is known to reduce hyperparathyroidism but there is little data to suggest any benefit on clinical outcomes (including CKD progression (measured by change in eGFR), all-cause mortality, cardiovascular mortality, cardiovascular events, fractures and hypercalaemia). Potential benefits of vitamin D therapy in people with CKD include increased bone mineral density and muscle strength, reduced risk of falls and fractures and reduction in hyperparathyroidism. Potential adverse effects are hypercalcaemia and extraskeletal (vascular) calcification, and increased cardiovascular risk.

Table 199: Criteria for selecting high-priority research recommendations

PICO question	In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes? Population: Adults aged 18+ with GFR 15-60 ml/min/1.73m^2 who are vitamin D deficient and have secondary hyperparathyroidism. Intervention: Vitamin D or vitamin D analogue Comparison: placebo Outcomes: • Composite outcome of falls and fracture risk • Health related quality of life

	• Mortality (all cause) • Cardiovascular events • Adverse events (including progression of CKD and hypercalcaemia (defined as serum calcium >2.5mmol/L)) • Hospitalisation Subgroup analysis: • Black, minority and ethnic groups • Older people aged >75years
Importance to patients or the population	CKD is common, vitamin D deficiency and secondary hyperparathyroidism develop early in the course of CKD and become increasingly prevalent at lower GFR levels. The prevalence of 25-hydroxy Vitamin D deficiency increasing from 9% in people with a GFR 60-89 to 27% in those with GFR<30 and the prevalence of hyperparathyroidism increasing from 9% to 74% in corresponding GFR groups. Observational data suggests an association between vitamin D deficiency and adverse patient related outcomes in people with CKD. To date there are no randomised controlled trial data comparing treatment with vitamin D and/or vitamin D analogues to no treatment in people with CKD in the prevention of adverse patient-related outcomes.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use of vitamin D and vitamin D analogues in the treatment of vitamin D deficiency and hyperparathyroidism in people with CKD
Relevance to the NHS	Vitamin D is cheap and vitamin D analogues are a relatively inexpensive therapy with the potential to reduce morbidity and mortality and increase quality of life in people with CKD, whilst reducing healthcare costs. Falls and fractures are expensive to the NHS and result in increased institutionalisation and increased consumption of healthcare resources.
National priorities	Reducing mortality considered amenable to healthcare and enhancing quality of life in people with long term conditions are 2 key domains in the NHS outcomes

	framework pertinent to this question.
Current evidence base	Native vitamin D obtained predominantly from exposure to sunlight undergoes hydroxylation in the liver and kidney to form activated vitamin D. It is known that as GFR declines activation of vitamin D is reduced. Abnormalities in circulating activated vitamin D, parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) are linked to an increased risk renal bone disease and bone fractures It is recommended that patients with vitamin D deficiency should be given cholecalciferol or ergocalciferol. (R1, section 1.5). However, there is insufficient and inconclusive evidence to support the routine use of nutritional or active vitamin D supplements for the management of renal bone disease in people with CKD (GFR 15-60). There is moderate evidence of harm, in the form of hypercalcaemia, in people treated with active vitamin D. Evidence found was of moderate to low quality mainly due to imprecision, missing data, as well as unclear allocation, concealment and randomisation processes. Publication dates ranged from 1988 (over twenty five years old) through to 2011. Some of the studies had a small patient population and many of the included studies were in people with secondary hyperparathyroidism. Overall the GDG considered that the follow-up periods in the reviewed studies were too short to show any long-term effects and were not powered to show reduction in falls or fracture.
Equality	Subgroup analysis has been specified because Vitamin D deficiency is more prevalent in black and Asian ethnic minorities for reasons which are only partially understood. Vitamin D deficiency is also more prevalent in older people and institutionalised people.
Study design	Randomised placebo controlled trial
Feasibility	Patients could be recruited from both primary and secondary care. As both CKD and vitamin D deficiency and secondary hyperparathyroidism are prevalent

	recruitment targets should be feasible. The main issue however would be to power the study to show a reduction in patient related outcomes such as reduction in falls or fractures.
Other comments	For simple vitamin D therapy and common analogues the trial is unlikely to attract commercial sponsors. However, given the size of the problem, the potential impact to patients and the NHS, and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding.
Importance	**High:** the research is relevant to the recommendations in this guideline and has potential overlap with other NICE guidance (hyperphosphataemia and osteoporosis).

N.4 Uric acid lowering agents

Research question: In people with CKD who are at high risk of progression, what is the clinical and cost effectiveness of uric acid lowering agents on the progression of CKD and on mortality?

Why this is important: CKD is a common long-term condition and both a low eGFR and raised ACR are powerful independent predictors of cardiovascular disease and progression to costly renal replacement therapy.

Uric acid excretion by the kidney involves different but related mechanisms: filtration, tubular reabsorption and tubular secretion. Urate is freely filtered at the glomerulus and then predominantly reabsorbed in the proximal tubule through an active anion-exchange process. Most urinary uric acid excreted is then derived from subsequent tubular secretion and uric acid accumulates as renal function diminshes.

Observational data have suggested that uric acid is an independent predictor of both progression and new incidence of CKD. It has also been proposed that elevated uric acid may have a role in initiating hypertension, arteriolosclerosis, insulin resistance and hypertriglyceridaemia. Hyperuricaemia is also associated with type 2 diabetes. It is difficult to infer causation from the observational data; is hyperuricaemia nephrotoxic or a marker of reduced eGFR? Is the relationship due to residual confounding?

The current randomised evidence for reducing uric acid in CKD patients is very limited and of poor quality, especially relating to the major outcomes of end stage kidney disease needing renal replacement therapy and mortality.

Table 200: Criteria for selecting high-priority research recommendations:

PICO question	For adults with CKD at high risk of progression does treatment with uric acid lowering therapy (allopurinol, febuxostat) reduce the risk of progression (primarily to end stage renal disease (ESRD) and mortality compared with placebo, and is this approach cost effective? Population: People with CKD at high risk of progression (people with cardiovascular disease, proteinuria, acute kidney injury, hypertension, diabetes, those who smoke, people of African, African–Caribbean or Asian family origin, those with chronic use of NSAIDs or those with untreated urinary outflow tract obstruction) Interventions: Allopurinol,febuxostat Comparators: placebo Outcomes: Mortality Progression (defined as ESRD) Progression (defined as change in eGFR) Change in antihypertensive use Health related quality of life
Importance to patients or the population	There is a body of evidence which supports the graded positive association of uric acid with progression of CKD (though not all studies find this) but it is unclear if this relationship is causative and whether reduction of uric acid would have benefits. There is some evidence of association with cardiovascular disease and mortality. There are a limited number of effective interventions to reduce risk of progression of CKD, primarily use of RAAS antagonists in patients with

	proteinuria and control of hypertension. Progression of CKD leads to cumulative morbidity, increasing risks of mortality, decrement in quality of life and function, and once ESKD is reached often need for costly renal replacement therapy. Given the shortage of kidneys for transplantation there are prolonged waits to receive a donor kidney, and a reliance on dialysis which is onerous, costly and has poor outcomes compared to the age matched general population. The major outcome for patents with CKD is cardiovascular mortality. Hence strategies to reduce the risks of both progression and cardiovascular disease in CKD are key. The absolute benefits of uric acid lowering will be greater in those at high risk of progression assuming there is a causal relationship. Factors associated with risk of progression are ACR, blood pressure, lower eGFR, as well as gender (male greater), younger age and ethnicity (greater south Asian, Black). There are few potential harms of treatment with allopurinol or febuxostat, these are chiefly related to allergy and certain specific drug interactions.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the use of uric acid lowering agents to prevent progression and reduce mortality in patients with CKD.
Relevance to the NHS	Allopurinol is a relatively inexpensive therapy with the potential to reduce morbidity and mortality and increase quality of life in people with CKD, whilst reducing healthcare costs, notably dialysis costs.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework.
Current evidence base	The current evidence is considered in paper 3 Asymptomatic hyperuricaemia GDG3 Dec 2012 3 RCTs of allopurinol vs.control/placebo were found in CKD patients, all were small and single centre (total patients 217) , of low quality, varying dose and follow-up duration was too short (<3 years). Bose et al NDT 2013 undertook a systematic review and meta-analysis of RCTs of

	uric acid lowering. 8 RCTs of allopurinol vs.placebo were included. There was no effect on progression in 5 trials reporting data on end of treatment GFR, however meta-analysis of 3 trials reporting creatinine data favoured uric acid lowering therapy. There were scant data on ESKD and mortality and the authors concluded that adequately powered randomised trial were required to evaluate the benefits and risks of uric acid lowering therapy in people with CKD.
Equality	Minority ethnic groups (Indo Asian, Black) and males are at higher risk of progression. Socio-economic status maybe too.
Study design	A randomised double-blind placebo-controlled trial is required to address this question. Patients could be recruited from primary care and secondary care. Inclusion: adults with CKD at high risk of progression (eGFR <45, ACR>30 mg/mmol, existing rate of progression above accepted age-related decline, diabetes, hypertension). Patients with symptomatic hyperuricaemia (acute gout and chronic tophaceous gout would be excluded. The intervention is Allopurinol 100 mg daily or Febuxostat 40 mg daily in those intolerant of Allopurinol versus placebo. The end-points should include: progression (change in kidney function), change in proteinuria, incident end stage kidney disease/start of renal replacement therapy, major cardiovascular events (composite); myocardial infarction; stroke; cardiovascular mortality; all-cause mortality; hospitalisation; health-related quality of life; change in serum uric acid concentration, use of hypertensive agents and change in blood pressure.
Feasibility	CKD is common, and hyperuricaemia is increasingly prevalent as GFR declines below 60 ml/min. The quality of general practice data in the UK, including albuminuria recording, are relatively high facilitating identification of people with CKD. Patients with low eGFR and albuminuria are likely to experience relatively high progression rates. There should be no particular ethical or technical issues.

Other comments	The trial is most unlikely to attract commercial sponsors. However, given the size of the problem, the potential impact to patients and the NHS, and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding.
Importance	This study is of high importance .

N.5 Renin-angiotensin-aldosterone system antagonists in people over 75 years

Research question: For people aged over 75 years with CKD, what is the clinical effectiveness of renin-angiotensin-aldosterone system (RAAS) antagonists?

Why this is important: RAAS antagonists are among the most commonly used drugs. They are recommended for people with CKD to reduce the rate of disease progression and mortality. The evidence for the use of RAAS antagonists is not specific to older people, so these recommendations are the same for all adults, regardless of age. However, there is a clinical suspicion that older people have a higher incidence of adverse effects from using RAAS antagonists, and uncertainty as to the balance of benefits and harm of using these agents in older people.

Table 201: Criteria for selecting high-priority research recommendations:

PICO question	In people over the age of 75 years with CKD who satisfy currently-recommended criteria for the use of RAAS-antagonists (with hypertension and ACR<30mg/mmol), what is the effect of use of these agents, compared to an alternative hypertension treatment regime, on important measurable outcomes (e.g. CKD progression, cardiovascular events, acute kidney injury, hospitalisation and health related quality of life) and mortality?
Importance to patients or the population	RAAS antagonists are recommended in the following circumstances relevant to older people with CKD: • diabetes and urine ACR≥3 mg/mmol • hypertension and urine ACR ≥30 mg/mmol • urine ACR ≥70 mg/mmol • resistant hypertension (where treatment with 3 or more drugs is

	required) • step 2 treatment for hypertension in those aged >55 years • chronic heart failure • post myocardial infarction. Most of these recommendations are based on evidence from studies which either exclude or contain a small minority of older people. Old people are at greater risk of adverse effects from RAAS-antagonists than are younger people. The most important adverse effect is acute kidney injury (AKI) which may arise from the haemodynamic effects of RAAS antagonists in the presence of renovascular disease (which is common in older people), or as a consequence of hypotension from over-treatment of hypertension, or as a result of impairment of RAAS-dependent renal compensatory mechanisms which then fail to function adequately when the individual is affected by dehydration, sepsis or hypotension. AKI can be fatal and often leads to permanent loss of renal function. The effect of RAAS antagonists on the incidence and severity of AKI in old people with CKD is not known. Neither is it known if the benefits of these agents in CKD, clearly demonstrable in younger patients, extend into old age. Current recommendations for use of RAAS antagonists in CKD take no account of age. It is therefore possible that, by following current recommendations based on evidence in younger people, older people come to harm.
Relevance to NICE guidance	If use of RAAS antagonists was shown to be associated with poorer outcomes in older people with CKD, NICE would be justified in stratifying guidance according to age (as in NICE guidance for management of hypertension 2011).
Relevance to the NHS	CKD is common, particularly in older age groups. If RAAS antagonists were shown to be inappropriate in older people with CKD, the likely impact of a revised recommendation would be: • Reduced prescriptions of RAAS antagonists in favour of cheaper

	alternatives • Reduced need for monitoring renal function • Reduced acute admissions with AKI or other adverse effects These changes to practice would all save financial and manpower resources
National priorities	Reduction in AKI is a national priority (National Service Framework for Renal Services part 2 (2005) and NCEPOD report "Adding Insult to Injury" 2009). Improving medical care of older people is the subject of a government white paper "Caring for our future: reforming care and support" (2012). With a growing population of older people, improving quality of care in this age group is included in the declared health delivery strategies of nearly every commissioning body.
Current evidence base	There is limited evidence avialble for those aged over 75. This was highlighted in CG73 and has been noted in the footnotes of the recommendations of the current guideline recommendations. The recommendations are largely based on extrapolated evidence from younger populations, as there is absence of evidence for this older age group specifically.
Equality	This research may allow recommendations to become more responsive to the specific needs of older individuals. The study design may need to take account of racial differences in response to RAAS antagonists.
Study design	Primary research is required. The study populations should consist of people over the age of 75 years with one of the following:- • diabetes and urine ACR≥3 mg/mmol • hypertension and urine ACR ≥30 mg/mmol • urine ACR ≥70 mg/mmol. Outcomes following treatment with RAAS antagonists should be investigated in one or several double-blind placebo-controlled clinical trials. Primary end-points should include hard outcomes such as all-cause mortality, cardiovascular events and progression to end-stage renal disease. Other relevant outcomes include

	rate of progression of CKD, quantification of proteinuria, hospital admission rate, incidence of AKI, falls and measures of quality of life.
Feasibility	This study should be highly feasible delivering useful outcomes in a short time-frame. The high prevalence of CKD in people aged over 75 facilitates recruitment. The interventions under investigation are already embedded in current practice and the important outcomes are common in this age group. Costs should therefore be acceptable. There are no particular ethical or technical issues.
Other comments	Since this research takes standard treatments as comparators, funding is unlikely to be forthcoming from a commercial source. Methodological problems include the need for risk stratification by comorbidity, which is a common problem in studies concentrating on older individuals. There will be a need for primary care engagement.
Importance	This research is of high importance. CKD is a common condition especially in older people. There is an unresolved clinical impression that the risks of using RAAS antagonists in old people may lead to significant morbidity and inappropriate use of health resources. Guideline-driven use of RAAS antagonists is one of only a handful of interventions for CKD which are included in the Quality Outcomes Framework (QOF). It is therefore important that the impact of this intervention on older people is fully understood and that subsequent guidance is properly evidenced.

Appendix O: Changes to recommendations from 2008 guideline

General changes

New recommendations 1.1.1 – 1.1.16: Clarification to terminology of GFR based on whether it is estimated, measured, based exclusively on serum creatinine results or cystatinC results (see introduction to the investigating CKD section for further details)

New recommendations 1.3.4, 1.6.3 - 1.6.14: Modified 'ACE inhibitor/ARB therapy' to use the term 'renin angiotensin system antagonists' so as to include renin inhibitors (the 3 classes of renin-angiotensin system antagonists are ACEi, ARBs and direct renin inhibitors).

New recommendations 1.6.12-1.6.14: The term 'plasma' was changed to 'serum' for consistency.

Table 202: Changes to recommendations from 2008 guideline

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
R1 1.1.1	Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of GFR (eGFR) using a prediction equation (see recommendation 1.1.2) in addition to reporting the serum creatinine result	Recommendation 1.1.1 in NICE guideline Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of glomerular filtration rate (eGFRcreatinine) using a prediction equation (see recommendation 1.1.2) in addition to reporting the serum creatinine result.[a] [2014]
R2 1.1.2	Use the IDMS (isotope dilution mass spectrometry)-traceable simplified MDRD (modification of diet in renal disease) equation to estimate GFR, using creatinine assays with calibration traceable to a standardised reference material. Ideally use creatinine assays that are specific and zero biased compared with IDMS (for example, enzymatic assays). When non-specific assays are used (for example, Jaffe assays), employ appropriate assay-specific adjustment factors to minimise between-laboratory variation (for example, those provided by national external quality assessment schemes).	Replaced by recommendation 1.1.2 in NICE guideline Clinical laboratories should: • use the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) creatinine equation to estimate GFRcreatinine, using creatinine assays with calibration traceable to standardised reference material • use creatinine assays that are specific (for example, enzymatic assays) and zero-biased compared with isotope dilution mass spectrometry (IDMS) • participate in a UK national external quality assessment scheme for creatinine. [new 2014]

[a] eGFRcreatinine may be less reliable in certain situations (for example, acute kidney injury, pregnancy, oedematous states, muscle wasting disorders, and in people who are malnourished or have had an amputation) and has not been well validated in certain ethnic groups (for example, in people of Asian family origin).

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
R3 1.1.3	Where indicated, apply a correction factor for ethnicity to reported GFR values (multiply eGFR by 1.21 for African-Caribbean ethnicity[4])	Replaced by recommendation 1.1.3 Apply a correction factor to GFR values estimated using the CKD-EPI creatinine equation for people of African–Caribbean or African family origin (multiply eGFR by 1.159). [new 2014]
R4 1.1.4	Interpret reported values of eGFR 60 ml/min/1.73 m^2 or more with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases.	Evidence reviewed but no change to recommendation 1.1.12 Interpret eGFR values of 60 ml/min/1.73 m^2 or more with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases. [2014]
R5 1.1.5	Where eGFR is simply reported as 60 ml/min/1.73 m^2 or more, use a rise in serum creatinine concentration of more than 20% to infer significant reduction in renal function.	Replaced by recommendation 1.1.11 If GFR is greater than 90 ml/min/1.73 m^2, use an increase in serum creatinine concentration of more than 20% to infer significant reduction in kidney function. [new 2014]
R6 1.1.6	Where a highly accurate measure of GFR is required (e.g. during monitoring of chemotherapy and in the evaluation of renal function in potential living donors), consider a gold standard measure (inulin, 51Cr-EDTA, 125I-iothalamate or iohexol).	Wording modified from 'gold standard' to 'reference standard' to highlight that there are a number of ways of direct measurement of GFR and that each of these methods is subject to variation and has limitations. Recommendation 1.1.16: Where a highly accurate measure of GFR is required – for example, during monitoring of chemotherapy and in the evaluation of renal function in potential living donors – consider a reference standard measure (inulin, ^{51}Cr-EDTA, ^{125}I-iothalamate or iohexol). [2008]
R7 1.1.7	In cases where there are extremes of muscle mass (e.g. body builders, amputees, muscle wasting disorders) interpret the eGFR with caution. (Reduced muscle mass will lead to overestimation and increased muscle mass to under-estimation).	Recommendation remains the same, although updated in line with NICE house style: Changes made to update NICE house style: 'cases' changed to 'people' and amputees changed to people who have had an amputation. Recommendation 1.1.4: In people with extremes of muscle mass – for example, in bodybuilders, people who have had an amputation or people with muscle wasting disorders – interpret eGFRcreatinine with caution. (Reduced muscle mass will lead to overestimation and increased muscle

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		mass to underestimation of the GFR.) [2008]
R8 1.1.8	Advise people not to eat any meat in the 12 hours before having a blood test for GFR estimation. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture.	Recommendation remains the same, although updated in line with NICE house style: Recommendation 1.1.5: Advise people not to eat any meat in the 12 hours before having a blood test for eGFRcreatinine. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture. [2008]
R9 1.1.9	An eGFR result less than 60 ml/min/1.73 m^2 in a person not previously tested should be confirmed by repeating the test within 2 weeks. Make an allowance for biological and analytical variability of serum creatinine (± 5%) when interpreting changes in eGFR.	Recommendation remains the same, although updated in line with NICE house style: Recommendation 1.1.13: Confirm an eGFR result of less than 60 ml/min/1.73 m^2 in a person not previously tested by repeating the test within 2 weeks. Allow for biological and analytical variability of serum creatinine (±5%) when interpreting changes in eGFR. [2008]
R10 1.1.17	When testing for the presence of haematuria, use reagent strips rather than urine microscopy. • Evaluate further if there is a result of 1+ or more. • Do not use urine microscopy to confirm a positive result.	Recommendation remains the same. Recommendation 1.1.23: When testing for the presence of haematuria, use reagent strips rather than urine microscopy. • Evaluate further if there is a result of 1+ or more. • Do not use urine microscopy to confirm a positive result. [2008]
R11 1.1.10	Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR.	Recommendation remains the same. Recommendation 1.1.17: Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. [2008]
R12 1.1.11	To detect and identify proteinuria, use urine ACR in preference, as it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of proteinuria, PCR can be used as an	Recommendation remains the same, although updated in line with NICE house style, and added ACR category. Recommendation 1.1.18: To detect and identify proteinuria, use urine ACR

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
	alternative. ACR is the recommended method for people with diabetes.	in preference to protein:creatinine ratio (PCR), because it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of levels of proteinuria of ACR 70 mg/mmol or more, PCR can be used as an alternative. ACR is the recommended method for people with diabetes. [2008, amended 2014]
R13 1.1.12	For the initial detection of proteinuria, if the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5 g/24 h or more) and less than 70 mg/mmol (approximately equivalent to PCR less than 100 mg/mmol, or urinary protein excretion less than 1 g/24 h) this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, or the PCR 100 mg/mmol or more, a repeat sample need not be tested.	Recommendation amended to: Recommendation 1.1.19: For the initial detection of proteinuria, if the ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested. [2008, amended 2014] The criteria for clinically significant proteinuria have been changed from an ACR of 30 mg/mmol to 3 mg/mmol. Although this question was not directly included in the update, the change came from evidence reviewed for the markers of kidney damage and classification of CKD sections. The GDG agreed that the risk of adverse outcomes is a continuum and starts at an ACR well below 30mg/mmol. The equivalences to PCR and urinary protein excretion were removed as the evidence showed that ACR was more accurate.
R14 1.1.13	In people without diabetes consider clinically significant proteinuria to be present when the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5 g/24 h or more).	Recommendation1.1.20: Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. The criteria for clinically significant proteinuria have been changed from an ACR of 30 mg/mmol to 3 mg/mmol. Although this question was not directly included in the update, the change came from evidence reviewed for the markers of kidney damage and classification of CKD sections. The GDG agreed that the risk of adverse outcomes is a continuum and starts at an ACR well below 30mg/mmol. There is a general move away from the term 'microalbuminuria' (ACR between 3-30mg/mmol) and the GDG wanted the

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		latest recommendations to reflect this.
R15 1.1.14	In people with diabetes consider microalbuminuria (ACR more than 2.5 mg/mmol in men and ACR more than 3.5 mg/mmol in women) to be clinically significant.	Replaced with recommendation 1.1.20: Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. The criteria for clinically significant proteinuria have been changed from an ACR of 30 mg/mmol to 3 mg/mmol. Although this question was not directly included in the update, the change came from evidence reviewed for the markers of kidney damage and classification of CKD sections. The GDG agreed that the risk of adverse outcomes is a continuum and starts at an ACR well below 30mg/mmol. There is a general move away from the term 'microalbuminuria' (ACR between 3-30mg/mmol) and the GDG wanted the latest recommendations to reflect this. Additionally it was no longer felt appropriate to have different criteria for gender. The GDG were not aware of any evidence on which the gender differences were based.
R16 1.1.15	All people with diabetes, and people without diabetes with a GFR less than 60 ml/min/1.73 m^2, should have their urinary albumin/protein excretion quantified. The first abnormal result should be confirmed on an early morning sample (if not previously obtained).	Recommendation 1.1.21: Quantify urinary albumin or urinary protein loss as in recommendation 1.1.18 for: • people with diabetes • people without diabetes with a GFR of less than 60 ml/min/1.73 m^2. [2008, amended 2014] Addition of bullet points and clarification of wording to make the recommendation clearer. The wording was changed from 'urinary albumin/protein excretion' to 'urinary albumin or urinary protein loss' as protein is lost rather than excreted. The second part of the original recommendation (regarding confirming on an early morning sample) was removed as it is already covered in recommendation 1.1.19

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		A reference to recommendation 1.1.18 was added regarding whether to use ACR or PCR.
R17 1.1.16	Quantify by laboratory testing the urinary albumin/protein excretion of people with an eGFR 60 ml/min/1.73 m ^{2}or more if there is a strong suspicion of CKD (see also recommendation 1.1.22).	Recommendation 1.1.22: Quantify by laboratory testing the urinary albumin or urinary protein loss of people with a GFR of 60 ml/min/1.73 m^2 or more if there is a strong suspicion of CKD (see also recommendation 1.1.28). [2008] The wording was changed from 'urinary albumin/protein excretion' to 'urinary albumin or urinary protein loss' as protein is lost rather than excreted.
R18 1.4.1	Offer a renal ultrasound to all people with CKD who: • have progressive CKD (eGFR decline more than 5 ml/min/1.73 m^2 within 1 year, or more than 10 ml/min/1.73 m^2 within 5 years) • have visible or persistent invisible haematuria • have symptoms of urinary tract obstruction • have a family history of polycystic kidney disease and are aged over 20 • have stage 4 or 5 CKD • are considered by a nephrologist to require a renal biopsy.	The first bullet point was modified to reflect the updated guideline definition of progression based on the evidence reviewed in the frequency of monitoring section (see recommendation 1.3.5). Recommendation 1.2.5: Offer a renal ultrasound scan to all people with CKD who: • have accelerated progression of CKD (see recommendation 1.3.3) • have visible or persistent invisible haematuria • have symptoms of urinary tract obstruction • have a family history of polycystic kidney disease and are aged over 20 years • have a GFR of less than 30 ml/min/1.73 m2 (GFR category G4 or G5) • are considered by a nephrologist to require a renal biopsy. [2008, amended 2014]
R19 1.4.2	Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them.	No changes to the recommendation. Recommendation 1.2.6: Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		ultrasound scan is arranged for them. [2008]
R20 1.2.1	Use the suffix '(p)' to denote the presence of proteinuria when staging CKD.	Deleted Recommendation deleted as recommendation 1.2.1 recommends using both GFR and ACR to stage CKD and so use of additional 'p' is not required.
R21 1.2.2	For the purposes of this classification define proteinuria as urinary ACR 30 mg/mmol or more, or PCR 50 mg/mmol or more (approximately equivalent to urinary protein excretion 0.5 g/24 h or more).	Recommendation 1.1.20: Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. [2008, amended 2014] The criteria for clinically significant proteinuria have been changed from an ACR of 30 mg/mmol to 3 mg/mmol. Although this question was not directly included in the update, the change came from evidence reviewed for the markers of kidney damage and classification of CKD sections. The GDG agreed that the risk of adverse outcomes is a continuum and starts at an ACR well below 30mg/mmol. There is a general move away from the term 'microalbuminuria' (ACR between 3-30mg/mmol) and the GDG wanted the latest recommendations to reflect this The equivalences to PCR and urinary protein excretion were removed as the evidence showed that ACR was more accurate.
R22 1.2.3	Stage 3 CKD should be split into two subcategories defined by: • GFR 45–59 ml/min/1.73m^2 (stage 3A), and • GFR 30–44 ml/min/1.73m^2 (stage 3B)	Deleted Recommendation deleted as this is now in common use and so recommendation not felt to be necessary. Also re-iterated in recommendation 1.2.1.
R23 1.2.4	At any given stage of CKD, management should not be influenced solely by age*. *In people aged over 70 years, an eGFR in the range 45–59 ml/min/1.73 m^2, if stable over time and without any other evidence of kidney damage, is unlikely to be associated with CKD-related complications.	Changed the recommendation to be more active and changed the word 'influenced' to 'determine' to improve the clarity of the recommendation. Recommendation 1.2.2: Do not determine management of CKD solely by age. [new 2014]
R24	Monitor GFR in people prescribed drugs known to be nephrotoxic such	Recommendation 1.1.27: Monitor GFR at least annually in people

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
1.1.21	as calcineurin inhibitors and lithium. Check GFR at least annually in people receiving long-term systemic non-steroidal anti-inflammatory drug (NSAID) treatment.	prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors (for example, cyclosporin or tacrolimus), lithium and non-steroidal anti-inflammatory drugs (NSAIDs). [2008, amended 2014] The frequency of monitoring was added for nephrotoxic drugs based on the British National Formulary which no longer indicates a difference in monitoring needs between NSAIDs and other nephrotoxic drugs. Annual monitoring was agreed by the GDG as appropriate for all of these drugs. Examples of calcineurin inhibitors were added for clarification.
R25 1.1.22	Offer people testing for CKD if they have any of the following risk factors: • diabetes • hypertension • cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease) • structural renal tract disease, renal calculi or prostatic hypertrophy • multisystem diseases with potential kidney involvement – for example, systemic lupus erythematosus • family history of stage 5 CKD or hereditary kidney disease • opportunistic detection of haematuria or proteinuria.	Replaced by recommendation 1.1.28 with addition of acute kidney injury from the new evidence review Offer testing for CKD using eGFRcreatinine and ACR to people with any of the following risk factors: • diabetes • hypertension • acute kidney injury (see recommendation 1.3.9) • cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease) • structural renal tract disease, renal calculi or prostatic hypertrophy • multisystem diseases with potential kidney involvement - for example, systemic lupus erythematosus • family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease • opportunistic detection of haematuria. [new 2014][b]

[b] This recommendation has been updated. However, the bullet points shaded in grey were not reviewed for this update and so we will not be able to accept comments on these.

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
R26 1.1.23	In the absence of the above risk factors, do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD.	Recommendation 1.1.29: Do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD. [2008, amended 2014] The initial part of the sentence 'In the absence of the above risk factors' was removed. The 2008 recommendation implied that if risk factors were present that age, gender and ethnicity could be considered as risk factors. The GDG did not find any evidence for this and agreed that rewording the recommendation promotes equality.
R27 1.5.1	Take the following steps to identify progressive CKD. • Obtain a minimum of three GFR estimations over a period of not less than 90 days. • In people with a new finding of reduced eGFR, repeat the eGFR within 2 weeks to exclude causes of acute deterioration of GFR – for example, acute kidney injury or initiation of ACE inhibitor/ARB therapy. • Define progression as a decline in eGFR of more than 5 ml/min/1.73 m^2 within 1 year, or more than 10 ml/min/1.73 m^2 within 5 years. • Focus particularly on those in whom a decline of GFR continuing at the observed rate would lead to the need for renal replacement therapy within their lifetime by extrapolating the current rate of decline.	New recommendation 1.3.3 was made to define accelerated progression of CKD. Recommendation 1.3.3: Define accelerated progression of CKD as: • a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months or • a sustained decrease in GFR of 15 ml/min/1.73 m2 per year. [new 2014] First two bullet points of the original recommendation were separated out as recommendation 1.3.4 to provide emphasis on the process to identify progressive CKD. Recommendation: 1.3.4: Take the following steps to identify the rate of progression of CKD: • Obtain a minimum of 3 GFR estimations over a period of not less than 90 days. • In people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR – for example,

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		acute kidney injury or initiation of renin–angiotensin system antagonist therapy. The third bullet point was updated as recommendation 1.3.5 based on evidence derived from the frequency of monitoring review which identified thresholds for progression. Recommendation 1.3.5: Be aware that people with CKD are at increased risk of progression to end-stage kidney disease if they have either of the following: • a sustained decrease in GFR of 25% or more over 12 months or • a sustained decrease in GFR of 15 ml/min/1.73 m^2 or more over 12 months. The GDG made a separate recommendation (1.3.6) from the fourth bullet point to give it additional focus, and clarified the wording according to NICE house style. Recommendation 1.3.6: When assessing CKD progression, extrapolate the current rate of decline of GFR and take this into account when planning intervention strategies, particularly if it suggests that the person might need renal replacement therapy in their lifetime.
R28 1.5.2	Work with people who have risk factors for progression of CKD to optimise their health. These risk factors are: • cardiovascular disease • proteinuria • hypertension • diabetes	Replaced by recommendation 1.3.7. 'Acute kidney injury' was added based on the 2014 evidence review. Modified wording for ethnicity based on NICE house style. Clarified that not all urinary outflow tract obstructions are risk factors, only those that are untreated (treatment will eliminate the risk of CKD progression). Recommendation 1.3.7: Work with people who have any of the following

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
	• smoking • black or Asian ethnicity • chronic use of NSAIDs • urinary outflow tract obstruction.	risk factors for CKD progression to optimise their health: • cardiovascular disease • proteinuria • acute kidney injury • hypertension • diabetes • smoking • African, African–Caribbean or Asian family origin • chronic use of NSAIDs • untreated urinary outflow tract obstruction. [new 2014]
R29 1.5.3	In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible fall in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression.	Recommendation remains the same, although updated in line with NICE house style. Recommendation 1.3.8: In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression. [2008]
R30 1.6.1	People with CKD in the following groups should normally be referred for specialist assessment: • stage 4 and 5 CKD (with or without diabetes) • higher levels of proteinuria (ACR 70 mg/mmol or more, approximately equivalent to PCR 100 mg/mmol or more, or urinary protein excretion 1 g/24 h or more) unless known to be due to diabetes and already appropriately treated	The first bullet point was amended to give GFR values rather than the stages to help clarify the criteria. In the second bullet point the equivalence to PCR value was removed to ensure consistency of ACR use. In the fourth bullet point the definition of progression was amended to the 2014 definition (see recommendation 1.3.5). The fifth bullet point was amended to cross reference the current NICE

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
	• proteinuria (ACR 30 mg/mmol or more, approximately equivalent to PCR 50 mg/mmol or more, or urinary protein excretion 0.5 g/24 h or more) together with haematuria • rapidly declining eGFR (more than 5 ml/min/1.73 m^2 in 1 year, or more than 10 ml/min/1.73 m^2 within 5 years) • hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses (see 'Hypertension: management of hypertension in adults in primary care' [NICE clinical guideline 34]) • people with, or suspected of having, rare or genetic causes of CKD • suspected renal artery stenosis.	guideline on hypertension. Recommendation 1.5.2: People with CKD in the following groups should normally be referred for specialist assessment: • GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes • ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated • ACR 30 mg/mmol (ACR category A3) or more, together with haematuria • sustained decrease in GFR of 25% or more and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months • hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also Hypertension [NICE clinical guideline 127]) • known or suspected rare or genetic causes of CKD • suspected renal artery stenosis. [2008, amended 2014]
R31 1.6.2	Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist.	No changes made to the recommendation. Recommendation 1.5.3: Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist. [2008]
R32 1.6.3	Once a referral has been made and a plan jointly agreed, it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified.	The text '(between the person with CKD or their carer and the healthcare professional)' was added to clarify who the plan should be agreed by. Recommendation 1.5.4: Once a referral has been made and a plan jointly agreed (between the person with CKD or their carer and the healthcare

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		professional), it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified. [2008]
R33 1.6.4	Take into account the individual's wishes and comorbidities when considering referral.	No change to recommendation wording, but this recommendation was put first in the section on referral criteria to give it more prominence. Recommendation 1.5.1: Take into account the individual's wishes and comorbidities when considering referral. [2008]
R34 1.6.5	People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload.	No change to recommendation: Recommendation 1.5.5: People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload. [2008]
R35 1.7.1	Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking.	No change to the recommendation. Recommendation 1.4.6: Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking. [2008]
R36 1.7.2	Where the clinician in discussion with the patient has decided that dietary intervention to influence progression of CKD is indicated, an appropriately trained professional should discuss the risks and benefits of dietary protein restriction, with particular reference to slowing down the progression of disease versus protein-calorie malnutrition.	Replaced by recommendation 1.4.9 after review of the evidence on low protein diets Recommendation 1.4.9: Do not offer low-protein diets (dietary protein intake less than 0.6–0.8 g/kg/day) to people with CKD. [new 2014]
R37 1.7.3	Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented.	No change to the recommendation Recommendation 1.4.8: Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented. [2008]
R38 1.7.4	Offer dietary advice to people with progressive CKD concerning potassium, phosphate, protein, calorie and salt intake when indicated.	Protein was removed because this was subject to a new evidence review. The GDG reworded the recommendation to state that advice should be

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		appropriate to the severity of CKD because 'progressive CKD' was considered to be ambiguous as it could refer to anyone with CKD. Recommendation 1.4.7: Offer dietary adviceabout potassium, phosphate, calorie and salt intake appropriate to the severity of CKD. [2008, amended 2014]
R39 1.8.1	In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg[6]	The text 'Existing hypertension guidelines such as the NICE hypertension guideline (NICE clinical guideline 34) give a range rather than just an upper limit and clinicians find this clear guidance useful.' was removed from the footnote because the current NICE guideline on hypertension does not provide ranges of blood pressure. Recommendation 1.6.1: In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.[c] [2008]
R40 1.8.2	In people with CKD and diabetes, and also in people with an ACR 70 mg/mmol or more (approximately equivalent to PCR 100 mg/mmol or more, or urinary protein excretion 1 g/24 h or more) aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg[6].	The PCR equivalence values were removed as the evidence suggests that ACR is more accurate. The text 'Existing hypertension guidelines such as the NICE hypertension guideline (NICE clinical guideline 34) give a range rather than just an upper limit and clinicians find this clear guidance useful.' was removed from the footnote because the current NICE guideline on hypertension does not provide ranges of blood pressure. Recommendation 1.6.2: In people with CKD and diabetes, and also in people with an ACR of 70 mg/mmol or more, aim to keep the systolic blood

[c] The GDG searched for and appraised evidence on blood pressure control, and did not set out to establish definitive safe ranges of blood pressure in CKD. The evidence presented in the full guideline does not therefore include safety of low blood pressure, but some such evidence does exist. The GDG set out a range of blood pressure targets, given in these recommendations, which in their clinical experience will inform good practice in CKD.

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg[d]. [2008]
R41 1.8.3	When implementing blockade of the renin-angiotensin system, start treatment with an ACE inhibitor first then move to an ARB if the ACE inhibitor is not tolerated.	Deleted Recommendation deleted as the evidence reviewed highlighted drugs should not be used together.
R42 1.8.4	Offer ACE inhibitors/ARBs to people with diabetes and ACR more than 2.5 mg/mmol (men) or more than 3.5 mg/mmol (women) irrespective of the presence of hypertension or CKD stage[7].	Replaced by recommendation 1.6.3: Offer a low-cost renin-angiotensin system antagonist to people with CKD and: • diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3) • hypertension and an ACR of 30 mg/mmol or more (ACR category A3) • an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease).[e] [new 2014]
R43 1.8.5	Offer ACE inhibitors/ARBs to non-diabetic people with CKD and hypertension and ACR 30 mg/mmol or more (approximately equivalent to PCR 50 mg/mmol or more, or urinary protein excretion 0.5 g/24 h or more)[7]	Replaced by recommendation 1.6.3: Offer a low-cost renin-angiotensin system antagonist to people with CKD and: • diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)

[d] The GDG searched for and appraised evidence on blood pressure control, and did not set out to establish definitive safe ranges of blood pressure in CKD. The evidence presented in the full guideline does not therefore include safety of low blood pressure, but some such evidence does exist. The GDG set out a range of blood pressure targets, given in these recommendations, which in their clinical experience will inform good practice in CKD.

[e] The evidence to support these criteria is limited in people aged over 70 years.

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		• hypertension and an ACR of 30 mg/mmol or more (ACR category A3) • an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease). [new 2014]
R44 1.8.6	Offer ACE inhibitors/ARBs to non-diabetic people with CKD and ACR 70 mg/mmol or more (approximately equivalent to PCR 100 mg/mmol or more, or urinary protein excretion 1 g/24 h or more) irrespective of the presence of hypertension or cardiovascular disease[7]	Replaced by recommendation 1.6.3: Offer a low-cost renin-angiotensin system antagonist to people with CKD and: • diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3) • hypertension and an ACR of 30 mg/mmol or more (ACR category A3) • an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease). [new 2014]
R45 1.8.7	Offer non-diabetic people with CKD and hypertension and ACR less than 30 mg/mmol (approximately equivalent to PCR less than 50 mg/mmol, or urinary protein excretion less than 0.5 g/24 h) a choice of antihypertensive treatment according to the NICE guidance on hypertension (NICE clinical guideline 34) to prevent or ameliorate progression of CKD.	Replaced by recommendation 1.6.5 Follow the treatment recommendations in Hypertension (NICE clinical guideline 127) for people with CKD, hypertension and an ACR of less than 30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes. [new 2014]
R46 1.8.8	When using ACE inhibitors/ARBs, titrate them to the maximum tolerated therapeutic dose before adding a second-line agent.	This recommendation was deleted. Recommendation deleted as the evidence reviewed highlighted drugs should not be used together.
R47 1.8.9	To improve concordance, inform people who are prescribed ACE inhibitors or ARB therapy about the importance of: • achieving the optimal tolerated dose of ACE inhibitor/ARB, and • monitoring eGFR and serum potassium in achieving this safely.	Recommendation 1.6.6: To improve concordance, inform people who are prescribed renin-angiotensin system antagonists about the importance of: • achieving the optimal tolerated dose of renin-angiotensin system antagonists and

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		• monitoring eGFR and serum potassium in achieving this safely. [2008]
R48 1.8.10	In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACE inhibitor/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACE inhibitor/ARB therapy and after each dose increase.	No changes made to the recommendation Recommendation 1.6.7: In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008]
R49 1.8.11	ACE inhibitor/ARB therapy should not normally be started if the pretreatment serum potassium concentration is significantly above the normal reference range (typically more than 5.0 mmol/litre).	The recommendation was amended for clarity and to reduce the uncertainty implied by changing 'significantly above the normal reference range' to 'greater than 5.0 mmol/litre'. Recommendation 1.6.8: Do not routinely offer a renin-–angiotensin system antagonist to people with CKD if their pre-treatment serum potassium concentration is greater than 5.0 mmol/litre. [2008, amended 2014]
R50 1.8.12	When hyperkalaemia precludes the use of ACE inhibitors/ARBs, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked.	No change to the recommendation. Recommendation 1.6.9: When hyperkalaemia precludes use of renin-angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked. [2008]
R51 1.8.13	Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of ACE inhibitors/ARBs, but be aware that more frequent monitoring of serum potassium concentration may be required.	No change to the recommendation. Recommendation 1.6.10: Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin-angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required. [2008]
R52	Stop ACE inhibitor/ARB therapy if the serum potassium concentration	No change to the recommendation.

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1.8.14	rises to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued.	Recommendation 1.6.11: Stop renin-angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued. [2008]
R53 1.8.15	Following the introduction or dose increase of ACE inhibitor/ARB, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the plasma creatinine increase from baseline is less than 30%.	No change to the recommendation. Recommendation 1.6.12: Following the introduction or dose increase of renin-angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%. [2008]
R54 1.8.16	If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACE inhibitor/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not modify the ACE inhibitor/ARB dose if the change in eGFR is less than 25% or the change in plasma creatinine is less than 30%.	No change to the recommendation. Recommendation 1.6.13: If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin-angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin-angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%. [2008]
R55 1.8.17	If the change in eGFR is 25% or more or the change in plasma creatinine is 30% or more: • investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (for example, NSAIDs) • if no other cause for the deterioration in renal function is found, stop the ACE inhibitor/ARB therapy or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required.	No change to the recommendation. Recommendation 1.6.14: If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more: • investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs) • if no other cause for the deterioration in renal function is found, stop the renin-angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required. [2008]

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R56 1.8.18	Where indicated, the use of ACE inhibitors/ARBs should not be influenced by a person's age as there is no evidence that their appropriate use in older people is associated with a greater risk of adverse effects.	Recommendation deleted. Content of the recommendation is already covered in recommendation 1.2.2.
R57 1.8.19	The use of statin therapy for the primary prevention[9] of cardiovascular disease (CVD)[9],[10]in people with CKD should not differ from its use in people without CKD and should be based on existing risk tables for people with and without diabetes. It should be understood that the Framingham risk tables significantly underestimate risk in people with CKD.	Replaced by recommendation 1.6.15. The NICE 'Lipid modification' guideline provides guidance on the use of statins in people with CKD and a reference to this guideline was considered appropriate. Recommendation 1.6.15:Follow the recommendations in Lipid modification (NICE clinical guidelin) for the use of statins in CKD.
R58 1.8.20	Offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values.	Replaced by recommendation 1.6.15. The NICE 'Lipids modification' guideline provides guidance on the use of statins in people with CKD and a reference to this guideline was considered appropriate. Recommendation 1.6.15:Follow the recommendations in Lipid modification (NICE clinical guideline) for the use of statins in CKD.
R59 1.8.21	Offer antiplatelet drugs to people with CKD for the secondary prevention of CVD. CKD is not a contraindication to the use of low dose aspirin but clinicians should be aware of the increased risk of minor bleeding in people with CKD given multiple antiplatelet drugs.	Replaced by recommendation 1.6.16: Offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. [new 2014]
R60 1.8.22	There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia.	This is not a recommendation.
R61 1.1.18	When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, regard two out of three positive reagent strip tests as confirmation of persistent invisible haematuria.	Recommendation remains the same, although updated in line with NICE house style. Recommendation 1.1.24: When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient

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		haematuria, regard 2 out of 3 positive reagent strip tests as confirmation of persistent invisible haematuria. [2008]
R62 1.1.19	Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups.	Recommendation remains the same, although updated in line with NICE house style. Recommendation 1.1.25: Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups. [2008]
R63 1.1.20	Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria/albuminuria (see recommendations above), GFR and blood pressure monitoring as long as the haematuria persists.	Recommendation remains the same, although updated in line with NICE house style. Recommendation 1.1.26: Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria (see recommendations 1.1.24 and 1.1.25), proteinuria or albuminuria, GFR and blood pressure monitoring as long as the haematuria persists. [2008]
R64 1.9.1	The routine measurement of calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with stage 1, 2, 3A or 3B CKD is not recommended.	No change to the recommendation, except to use GFR categories instead of stages. Recommendation 1.7.1: Do not routinely measure calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people witha GFR of 30 ml/min/1.73 m2 or more (GFR category G1, G2 or G3). [2008]
R65 1.9.2	Measure serum calcium, phosphate and PTH concentrations in people with stage 4 or 5 CKD (GFR less than 30 ml/min/1.73 m^2). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists seek specialist opinion.	No change to the recommendation except to use GFR categories instead of stages. Recommendation 1.7.2: Measure serum calcium, phosphate and PTH concentrations in people witha GFR of less than 30 ml/min/1.73 m2 (GFR category G4 or G5). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists, seek specialist opinion. [2008]

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R66 1.9.3	Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with stage 1, 2, 3A or 3B CKD.	No change to the recommendation, except to use GFR categories instead of stages. Recommendation 1.7.3: Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people witha GFR of 30 ml/min/1.73 m2 or more (GFR category G1, G2 or G3). [2008]
R67 1.9.4	When vitamin D supplementation is indicated in people with CKD offer: • cholecalciferol or ergocalciferol to people with stage 1, 2, 3A or 3B CKD • 1-alpha-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol) to people with stage 4 or 5 CKD.	Replaced by recommendations 1.7.5 and 1.7.6: Recommendation 1.7.5: Offer colecalciferol or ergocalciferol to treat vitamin D deficiency in people with CKD and vitamin D deficiency. [new 2014] Recommendation 1.7.6: If vitamin D deficiency has been corrected and symptoms of CKD-mineral and bone disorders persist, offer alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol (1-25-dihydroxycholecalciferol) to people witha GFR of less than 30 ml/min/1.73 m2 (GFR category G4 or G5). [new 2014]
R68 1.9.5	Monitor serum calcium and phosphate concentrations in people receiving 1-alpha-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol supplementation.[11]	Evidence reviewed but no change to the recommendation. Recommendation 1.7.7: Monitor serum calcium and phosphate concentrations in people receiving alfacalcidol or calcitriol supplements. [2014]
R69 1.9.6	If not already measured, check the haemoglobin level in people with stage 3B, 4 and 5 CKD to identify anaemia (Hb less than 11.0 g/dl, see 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 39]). Determine the subsequent frequency of testing by the measured value and the clinical circumstances.	Modified link to Anaemia management in CKD guideline. Recommendation 1.7.8: If not already measured, check the haemoglobin level in peoplewith a GFR of less than 45 ml/min/1.73 m2 (GFR category G3b, G4 or G5) to identify anaemia (haemoglobin less than 110 g/litre (11.0g/dl), see Anaemia management in people with chronic kidney disease [NICE clinical guideline 114]). Determine the subsequent frequency of testing by the measured value and the clinical circumstances. [2008]
R70	Offer people with CKD education and information tailored to the stage	No change to recommendation, except to replace the term ‘stage’ with

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
1.3.1	and cause of CKD, the associated complications and the risk of progression.	'severity'. Recommendation 1.4.1: Offer people with CKD education and information tailored to the severity and cause of CKD, the associated complications and the risk of progression**.** [2008]
R71 1.3.2	When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested. • What is CKD and how does it affect people? • What questions should people ask about their kidneys when they attend clinic? • What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication? • What can people do to manage and influence their own condition? • In what ways could CKD and its treatment affect people's daily life, social activities, work opportunities and financial situation, including benefits and allowances available? • How can people cope with and adjust to CKD and what sources of psychological support are available? • When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and pre-emptive transplantation) and the preparation required (such as having a fistula or peritoneal catheter). • Conservative management may be considered where appropriate.	The second bullet point (What questions should people ask about their kidneys when they attend clinic?) was changed to simplify and recognise that the provision of services has changed. Recommendation 1.4.2: When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested. • What is CKD and how does it affect people? • What questions should people ask about their kidneys? • What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication? • What can people do to manage and influence their own condition? • In what ways could CKD and its treatment affect people's daily life, social activities, work opportunities and financial situation, including benefits and allowances available? • How can people cope with and adjust to CKD and what sources of psychological support are available? • When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and pre-emptive transplantation) and the preparation required (such as having a fistula or peritoneal catheter).

Old No	Old recommendation wording	Reason for deletion/Reason for editing/ Destination in new guideline
		• Conservative management and when it may be considered . [2008]
R72 1.3.3	Offer people with CKD high quality information or education programmes at appropriate stages of their condition to allow time for them to fully understand and make informed choices about their treatment.	No change to the recommendation, except to replace the term 'stage' with 'severity'. Recommendation 1.4.3: Offer people with CKD high-quality information or education programmes as appropriate to the severity of their condition to allow time for them to fully understand and make informed choices about their treatment. [2008]
R73 1.3.4	Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning.	No change to the recommendation. Recommendation 1.4.4: Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning. [2008]
R74 1.3.5	Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support – for example, support groups, counselling or a specialist nurse.	No change to the recommendation. Recommendation 1.4.5: Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support – for example, support groups, counselling or a specialist nurse. [2008]

Appendix P: Deleted content from 2008 guideline

Preface

Chronic kidney disease (CKD) is of growing importance in the UK. The NHS is increasingly focussing on prevention and on the early detection and treatment of potentially progressive disease, whilst the prevalence of risk factors for CKD, such as diabetes, obesity and hypertension is rising. It is therefore a great pleasure to introduce this timely new guideline on CKD from the National Collaborating Centre for Chronic Conditions (NCC-CC) and the National Institute for Health and Clinical Excellence (NICE).

The recommendations you will read here are the result of a thorough review of the published research. The field of renal medicine has a complex evidence base, and enormous thanks are due to the Guideline Development Group for their hard work and attention to detail, and to the NCC-CC Technical Team who worked enthusiastically alongside them. As for all our guidelines, full evidence tables summarising the clinical evidence base, and full details of the health economic modelling, are available from the Royal College of Physicians' website. Readers involved in research in this field, and those who want to find the full rationale behind a particular recommendation, will find this an invaluable resource.

The Department of Health, in commissioning this guideline, was clear that the focus was to be on early detection and management. This is the area in which the guideline can deliver its greatest potential benefit, through delaying progression of disease and thus reducing the need for dialysis or transplantation. The key priority recommendations singled out in the guideline reflect this emphasis. They present clear criteria for testing for CKD, suspecting progressive CKD, and referring people for specialist assessment, all of which should be useful in primary care. Recommendations are also provided on starting treatment once proteinuria has been assessed.

In common with other guideline topics in chronic conditions, there are some areas in CKD which remain in need of good quality research to inform difficult clinical decisions. The GDG have not shirked from addressing these questions and their expertise informed debates which led to some forward-thinking recommendations, for example those dealing with testing for proteinuria. For many practitioners a change in practice will be required as a result, but great effort has been taken to explain the rationale for this change within the guideline, and to demonstrate that the necessary effort is worthwhile.

As healthcare professionals in primary care take on an increasing role in the management of CKD, it is hoped that this guideline will be a single useful and accessible reference promoting a consistent high quality of care and hence improved quality of life for longer for people with CKD.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

P.1 Section 1: Introduction

P.1.1 Section 1.1: Background

Publication of the second part of the Renal National Service Framework (NSF)[161] served to emphasise the change in focus in renal medicine from treatment of established kidney disease to earlier identification and prevention of kidney disease. Allied to this is the knowledge that late referral of people with advanced kidney disease to nephrology services from both primary and secondary care is still at least as high as 30%, engendering increased mortality and morbidity[41,300,323,368,562,625] and precluding assessment and preparation of those for whom conservative management is more appropriate.

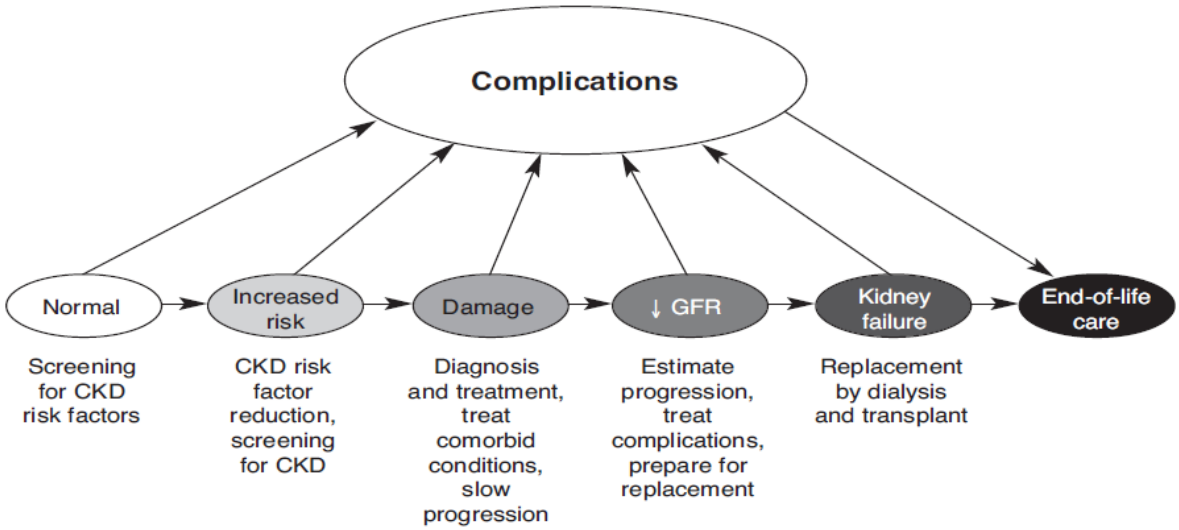
Over 2% of the total NHS budget is spent on renal replacement therapy (dialysis and transplantation) for those with established renal failure.[36] Strategies aimed at earlier identification and (where possible) prevention of progression to established renal failure are therefore clearly required. Equally importantly, population studies have shown that people with diagnosed chronic kidney disease (CKD) have a far greater likelihood of cardiovascular death than progression to established renal failure.[169,229,319,333] Furthermore, the majority of people with CKD are asymptomatic and may not even be aware that they have any form of kidney problem.

The challenge is to:

- identify people with or at risk of developing CKD
- determine who needs intervention to minimise cardiovascular risk and to determine what that intervention should comprise
- determine who will develop progressive kidney disease and/or complications of kidney disease and how they may be identified and managed to reduce/prevent these outcomes
- determine who needs referral for specialist kidney care.

This requires adoption of an overall health approach (Figure 269) and an integrated care strategy involving public awareness, professional education, policy influence, and improved care delivery systems all under-pinned by research.

Figure 269: Chronic kidney disease: an overall health approach



GFR = glomerular filtration rate.

Source: Reprinted by permission from Macmillan Publilshers Ltd: Lodney International, Levey AS, Atkins R, Coresh J et al. Chronic kidney disease as a global health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. Kidney IOnterational 2007; 72(3): 247-259. Copyright 2007[376]

A key component of the integrated care strategy is development of clinical guidelines which synthesise a scientific understanding of the disease in terms of:

- the disease prevalence
- the ability to identify the disease and the people at risk
- a knowledge of best therapies and strategies
- the ability to deliver effective therapies in the right place at the right time with the right tools.

In March 2006 the Joint Specialty Committee of the Royal College of Physicians of London and the Renal Association, together with representatives from the Royal College of General Practitioners, the Association for Clinical Biochemistry, the Society for District General Hospital Nephrologists, the British Geriatric Society, the Professional Advisory Council of Diabetes UK and the National Kidney Federation produced guidelines for the identification, management and referral of adult people with CKD.[589] Two further national strategies promoting identification of CKD were implemented in April 2006: the automatic reporting of an estimated glomerular filtration rate (eGFR) whenever a serum creatinine measurement is requested of any clinical chemistry laboratory[163] and the introduction of 4 renal domains in the Quality and Outcomes Framework (QOF) subsequently updated in April 2008 (Table 203)[7] These national strategies have raised questions that this guideline attempts to answer whilst addressing the challenges detailed above.

Table 203: Quality and Outcomes Framework Guidance Chronic Kidney Disease Indicator Set (updated April 2008)

Indicator 1	**The practice can produce a register of patients aged 18 years and over with CKD (US National Kidney Foundation: Stage 3–5 CKD)**

Indicator 1	The practice can produce a register of patients aged 18 years and over with CKD (US National Kidney Foundation: Stage 3–5 CKD)
Indicator 2	The percentage of patients on the CKD Register whose notes have a record of blood pressure in the previous 15 months
Indicator 3	The percentage of patients on the CKD Register in whom the last blood pressure reading, measured in the previous 15 months, is 140/85 or less
Indicator 5	The percentage of patients on the CKD Register with hypertension and proteinuria who are treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) (unless a contraindication or side effects are recorded)

P.1.2 Section 1.2: Definition

The Renal NSF adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD. This classification divides CKD into five stages (Table 204) defined by evidence of kidney damage and level of renal function as measured by glomerular filtration rate (GFR). Stages 3–5 may be defined by GFR alone, whilst stages 1 and 2 also require the presence of persistent proteinuria, albuminuria, haematuria or structural abnormalities. Stage 5 CKD may be described as established renal failure (also called end stage renal failure (ESRD)), and is CKD which has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) may be required to maintain life. Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only.

The classification of CKD into 5 stages has been widely adopted but as understanding of the epidemiology of CKD has developed, it has been criticised as not being sufficiently sophisticated for clinical needs. For example, longitudinal population studies have suggested that stage 3 should be subdivided into 3A and 3B. Other studies, underlining the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes in CKD, suggest the adoption of a '(p)' suffix in the different stages. This evidence and the changes to the classification that the evidence suggests will be considered further in the relevant sections of the guideline.

Table 204: NKF-KDOQI stages of chronic kidney disease

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60–89
3*	Moderate reduction in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure	<15 (or dialysis)

** This guideline recommends splitting this into 3A and 3B – see classification section.*

CKD is defined as either kidney damage (proteinuria, haematuria or anatomical abnormality) or GFR <60 ml/min/1.73m^2 present on at least 2 occasions for ≥3 months.

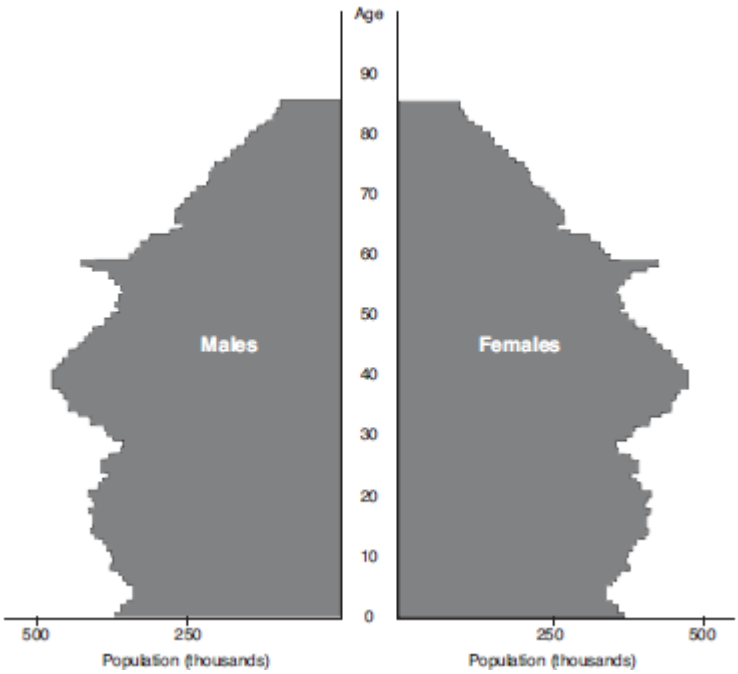
P.1.3 Section 1.3: Burden of disease

CKD is increasingly recognised as a public health problem and is usually characterised by an asymptomatic period, which is potentially detectable. Tests for detecting CKD are both simple and

freely available and there is evidence that treatment can prevent or delay progression of CKD, reduce or prevent development of complications, and reduce the risk of cardiovascular disease (CVD). There is considerable overlap between CKD, diabetes and CVD and the risk of developing CKD increases with increasing age. In assessing the burden of disease it is important to understand the characteristics of our population.

The UK is an ageing and growing population. Since 1971 the population has increased by 7.7% and since 2001 by 0.5% per annum such that the UK population in 2005 numbered 60,209,500 people.[505] The mean age of the population in 1971 was 34.4 years and that had increased to 38.8 years with 16% of the population over 65 years of age in 2005 (Figure 270). The population is also gaining weight; 67% of men and 58% of women are overweight. The population prevalence of diabetes is 4%; 11.3% of the population are hypertensive; and although smoking rates have decreased, 24% of the population aged over 16 are smokers (25% of men and 23% of women). It is unsurprising that CVD remains prevalent: 3.6% of the population have coronary heart disease, 1.5% cerebrovascular disease, and 0.4% congestive heart failure.

Figure 270: Age and gender distribution of the UK population in 2005



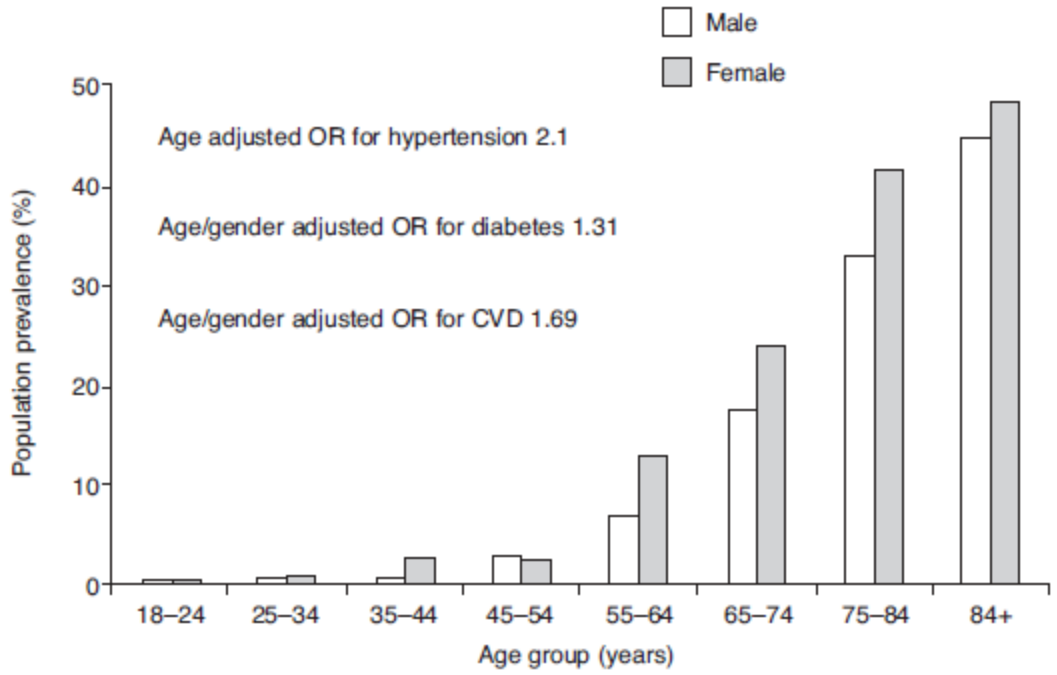
Source: Office for National Statistics website: www.ons.gov.uk. Crown copyright material is reproduced with the permission of the Controller Office of Public Sector Information (OPSI). Reproduced under the terms of the Click-Use Licence.

Data from the UK Renal Registry[36] indicate that there were 41,776 adult patients alive on renal replacement therapy (RRT) in the UK at the end of 2005, a prevalence for adults of 694 per million population (pmp). Addition of the 748 children under age 18 on RRT gives a total prevalence of 706 pmp. There was a 5.0% annual increase in the prevalence of people on RRT in the 38 renal units participating in the Registry since 2000. In 2005, the mean percentage of patients referred late (less than 90 days before dialysis initiation) was still 30%, unchanged from the value in 2000.

Whilst the UK Renal Registry provides accurate estimates of numbers of people undergoing RRT, this cannot be seen as a surrogate for the number of people with stage 5 CKD, as the mean GFR of those starting RRT is 7.5 ml/min/1.73m^2.

Information relating to the UK population prevalence of stage 3–5 CKD comes from a large primary care study (practice population 162,113) suggesting an age standardised prevalence of stage 3–5 CKD of 8.5% (10.6% in females and 5.8% in males). In these people the age- and gender-adjusted odds ratio for hypertension was 2.1 (95% CI 2.0–2.2), for diabetes 1.33 (95% CI 1.21–1.41) and for CVD 1.69 (95% CI 1.59–1.79).[653] The prevalence of CKD rose dramatically with age (Figure 271).

Figure 271: Adult CKD prevalence in the UK: age-standardised prevalence of stage 3-5 ≈ 8.5%



Source: (Reprinted by permission from Macmillan Publishers Ltd: Kidney International (Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney International 2007; 72(1):92–99). [653] *Copyright 2007.*

Although we have very little information about the total burden of CKD in the UK, data from the National Health and Nutrition Examination Surveys (NHANES)[108,139] in the USA not only gives a guide to the likely overall population prevalence, but also suggests that the prevalence is increasing. Comparison of the prevalence of CKD in NHANES 1988–1994 with NHANES 1999–2004 showed an increase in population prevalence from 10.03 to 13.07%.[140] The overall prevalence among men increased from 8.2% to 11.1% and in women from 12.1% to 15.0%. The increased prevalence was partly explained by the increase in a number of CKD risk factors, including an ageing population and an increase in obesity, diagnosed diabetes and hypertension. It is important to note that the NHANES studies included only non-institutionalised people, and the prevalence of CKD in nursing homes is likely to be significantly higher.

UK population studies have demonstrated that the risk of cardiovascular death in people with diagnosed CKD far outweighs the risk of progression. A retrospective cohort study found that only 4% of 1076 individuals progressed to end stage kidney disease over a 5.5 year follow-up period whilst 69% had died at the end of follow-up; the cause of death was cardiovascular in 46% of cases.[169] Similarly, a prospective cohort study of 3240 individuals with a median GFR of 28.5 ml/min/1.73m^2 not known to renal services found that mortality was 39.5% after a median follow-up period of 31.3 months. The cause of death was cardiovascular in 39.7% of cases. Only 8.3% of individuals sustained a decline in GFR greater than 5 ml/min/1.73m^2/year during the period of follow-up.[319] This remarkable burden of cardiovascular disease in people with CKD, and the relative lack of progression, has been confirmed in a number of observational studies[229,333] and is further illustrated by results from the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project where 50% of those with a stage 4 and 5 CKD had coexistent CVD which increased in prevalence as GFR decreased.[653] The magnitude of other comorbidities such as diabetes, hypertension and significant anaemia also increased with more advanced kidney dysfunction (Table 205).

Table 205: NEORICA: Comorbidity stratified by GFR

GFR (ml/min/1.73m^2)	**<30** N=525	**30–44** N=2475	**45–59** N=8731	**>60** N=26531
All CVD (%)	50.7	42.7	27.1	14.8
Diabetes (%)	23.0	16.1	12	9.4
Hypertension (%)	87.8	86.6	71.4	47.1
Haemoglobin (Hb) <11 g/dl (%)	10.0	4.1	2.9	2.7

Source: Adapted and reprinted by permission from Macmillan Publishers Ltd: Kidney International (Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney International 2007; 72(1):92–99). [653] *Copyright 2007.*

The study of unreferred CKD by John et al. demonstrated that 85% of those with advanced kidney dysfunction were unknown to renal services.[319] The NEOERICA study serves to underline this but also demonstrates that CKD is still largely unrecognised: only 2.1% of those with a GFR less than 60 ml/min/1.73m^2 had a coded diagnosis of renal disease.

A national programme to identify vulnerability to vascular diseases was announced by the Secretary of State for Health in April 2008 following initial results from modelling work carried out by the Department of Health. This work suggested that a vascular check programme would prevent 4000 people a year from developing diabetes and could also detect at least 25,000 cases of diabetes or kidney disease earlier.

It has long been recognised that the prevalence of established renal failure is higher amongst the black and minority ethnic communities in comparison to Caucasian populations.[581] The predominant reasons for this include the increased prevalence of Type 2 diabetes in South Asians and hypertension in African Caribbeans, together with diseases particular to certain communities such as chronic interstitial nephritis in South Asians and focal glomerulosclerosis in African Caribbeans. However, there is a relative lack of knowledge concerning the prevalence of earlier stages of CKD in black and ethnic minority populations in comparison to Caucasians. In the United States, the racial disparity in the incidence of established renal failure among black compared with white populations

is not reflected in the prevalence of less severe degrees of impaired kidney function.[436] Similar findings have been reported from the NHANES III data. It has been suggested that the reasons for this disparity lie with racial differences in the rate of progression to established renal failure. The ABLE projects (A Better Life through Education and Empowerment) in the UK have also demonstrated that kidney disease in South Asians and African Caribbeans may deteriorate more rapidly to established renal failure.[340] In the long term, the ABLE study aims to identify the reasons for this faster deterioration.

P.2 Section 2: Methodology

P.2.1 Section 2.1: Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for the early identification and management of CKD in adults in primary and secondary care
- is based on best published clinical and economic evidence, alongside expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for CKD
- details areas of uncertainty or controversy requiring further research and
- provides a choice of guideline versions for different audiences.

P.2.2 Section 2.2: Scope

The guideline was developed in accordance with a scope which detailed the remit of the guideline originating from the Department of Health and specified those aspects of CKD care to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE).[477] The full scope is shown in Appendix B.

P.2.3 Section 2.3: Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with CKD and their carers
- patient support groups
- commissioning organisations and
- service providers.

P.2.4 Section 2.4: Involvement of people with CKD

The NCC-CC was keen to ensure the views and preferences of people with CKD and their carers informed all stages of the guideline. This was achieved by:

- having a person with CKD and a carer as patient representatives on the guideline development group
- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project and
- the inclusion of patient groups as registered stakeholders for the guideline.

P.2.5 Section 2.5: Guideline limitations

Guideline limitations are as follows:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature review of all pharmacological toxicity. NICE expects the guidelines to be read alongside the summaries of product characteristics.

P.2.6 Section 2.6: Other work relevant to the guideline

Related NICE public health guidance comprises:

- 'Brief interventions and referral for smoking cessation in primary care and other settings'.[474]

Related NICE clinical guidelines are:

- 'Anaemia management in chronic kidney disease'[473]
- 'Hypertension: management of hypertension in adults in primary care'[475]
- 'Type 2 diabetes: the management of type 2 diabetes (update)' [480]
- 'Lipid modification: cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'[478]
- 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.[479]

P.2.7 Section 2.8: The process of guideline development

Evidence tables are available on-line at http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257

7. Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate and
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on:

- recommendations as key priorities for implementation
- key research recommendations and
- algorithms.

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation in practice
- more efficient use of NHS resources and
- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced by NICE following publication in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

8. Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- Clinical introduction: sets a succinct background and describes the current clinical context
- Methodological introduction: describes any issues or limitations that were apparent when reading the evidence base
- Evidence statements: provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest
- Health economics: presents, where appropriate, an overview of the cost effectiveness evidence-base, or any economics modelling
- From evidence to recommendations: sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations
- Recommendations: provides stand alone, action-orientated recommendations
- Evidence tables: The evidence tables are not published as part of the full guideline but are available online at http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

9. Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website, www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The different versions of the guideline are shown in Table 206.

Table 206: Different versions of the guideline

Full version	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257
NICE version	Documents the recommendations without any supporting evidence. Available at http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257
'Quick reference guide'	An abridged version. http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257
'Understanding NICE guidance'	A lay version of the guideline recommendations http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257

10. Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 8 February 2008 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately four years after publication.

P.2.8 Section 2.9: Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

P.2.9 Section 2.10: Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

P.3 Section 3: Key messages of the guideline

P.3.1 Section 3.1: Key priorities for implementation

- To detect and identify proteinuria, use albumin:creatinine ratio (ACR) in preference, as it has greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria. For quantification and monitoring of proteinuria, PCR can be used as an alternative. ACR is the recommended method for people with diabetes.

Offer ACEI/ARBs to non-diabetic people with CKD and hypertension and ACR ≥30 mg/mmol (approximately equivalent to PCR ≥50 mg/mmol, or urinary protein of ≥0.5 g/day).

Stage 3 CKD should be split into two subcategories defined by:

- GFR 45–59 ml/min/1.73m^2 (stage 3A)
- GFR 30–44 ml/min/1.73m^2 (stage 3B).

People with CKD should usually be referred for specialist assessment if any of the following apply:

- stage 4 and 5 CKD (with or without diabetes)
- heavy proteinuria (ACR ≥70 mg/mmol, approximately equivalent to PCR ≥100 mg/mmol , or urinary protein excretion ≥1 g/24 h) unless known to be due to diabetes and already appropriately treated
- proteinuria (ACR ≥30 mg/mmol, approximately equivalent to PCR ≥50 mg/mmol, or urinary protein excretion ≥ 0.5 g/24 h) together with haematuria
- rapidly declining eGFR (>5 ml/min/1.73m^2 in one year, or >10 ml/min/1.73m^2 within 5 years)
- hypertension that remains poorly controlled despite the use of at least 4 anti-hypertensive drugs at therapeutic doses (see NICE clinical guideline 34, 'Hypertension: management of hypertension in adults in primary care')
- a rare or genetic cause of CKD, or the suspicion of one
- suspected renal artery stenosis.

Offer people testing for CKD if they have any of the following risk factors:

- diabetes (types 1 and 2)
- hypertension
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
- structural renal tract disease, renal calculi or prostatic hypertrophy
- multi-system diseases with potential kidney involvement, e.g. SLE
- family history of stage 5 CKD or hereditary kidney disease.

Take the following steps to identify progressive CKD:

- Obtain a minimum of three glomerular filtration rate (GFR) estimations are required over a period of not less than 90 days
- in people with a new finding of reduced eGFR, repeat the estimated glomerular filtration rate (eGFR) within 2 weeks to exclude causes of acute deterioration of GFR, e.g. acute kidney injury or initiation of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy
- define progression as a decline in eGFR of >5 ml/min/1.73m^2 within one year, or >10 ml/min/1.73m^2 within 5 years
- focus particularly on those in whom a rate of decline of GFR continuing at the observed rate would lead to the need for renal replacement therapy within their lifetime by extrapolating the current rate of decline.

In people with CKD, aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.

P.3.2 Section 3.2: Algorithms

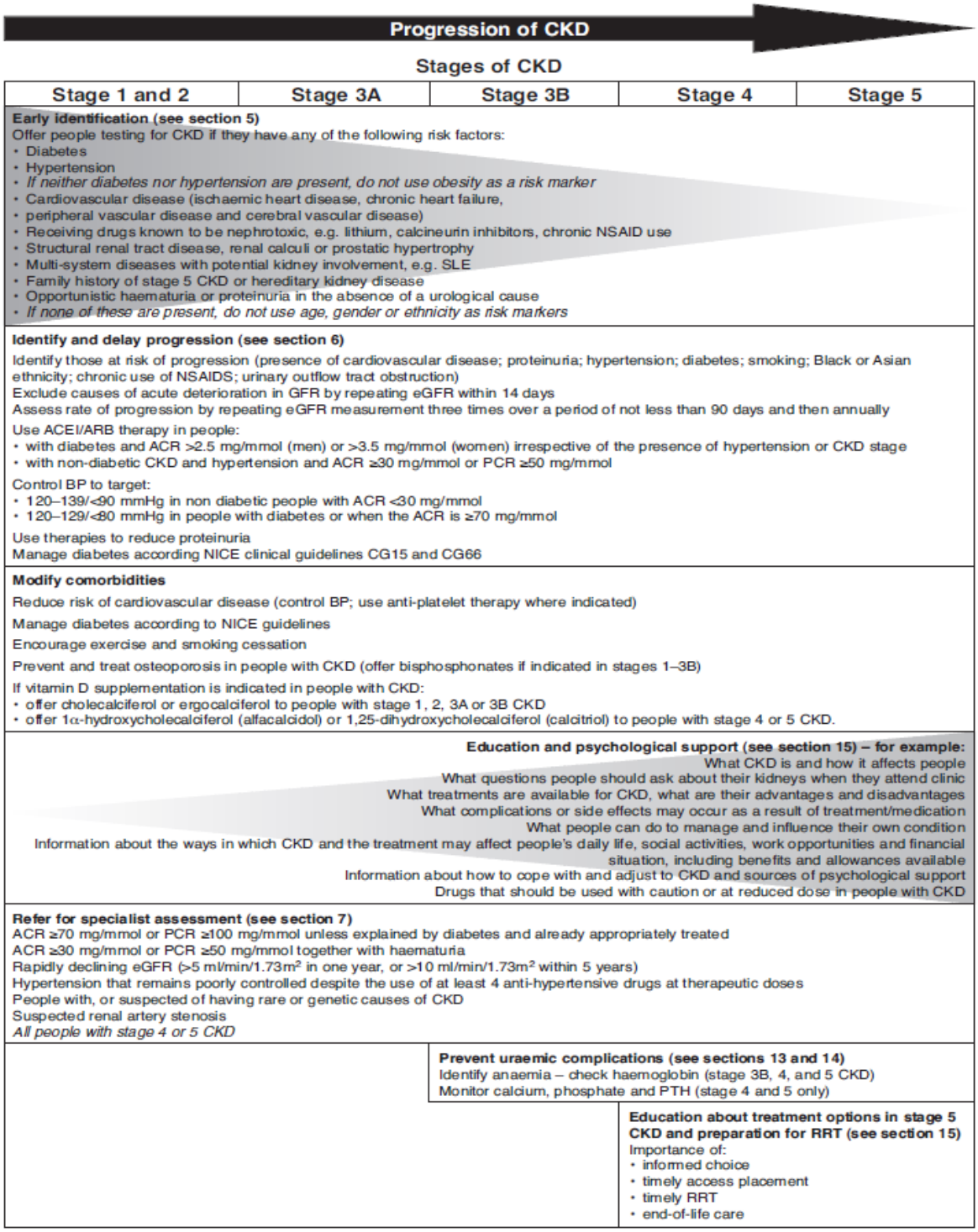
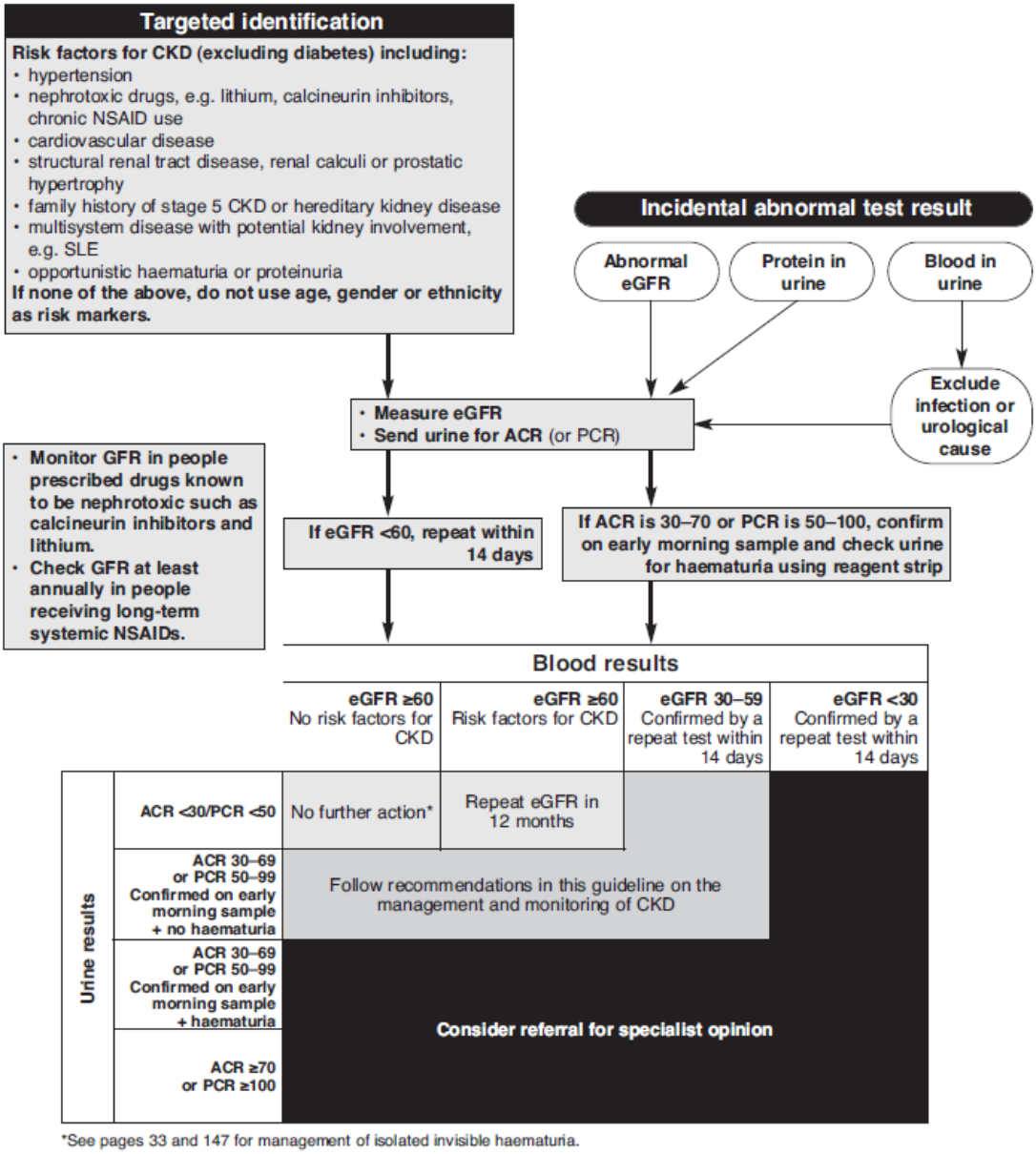
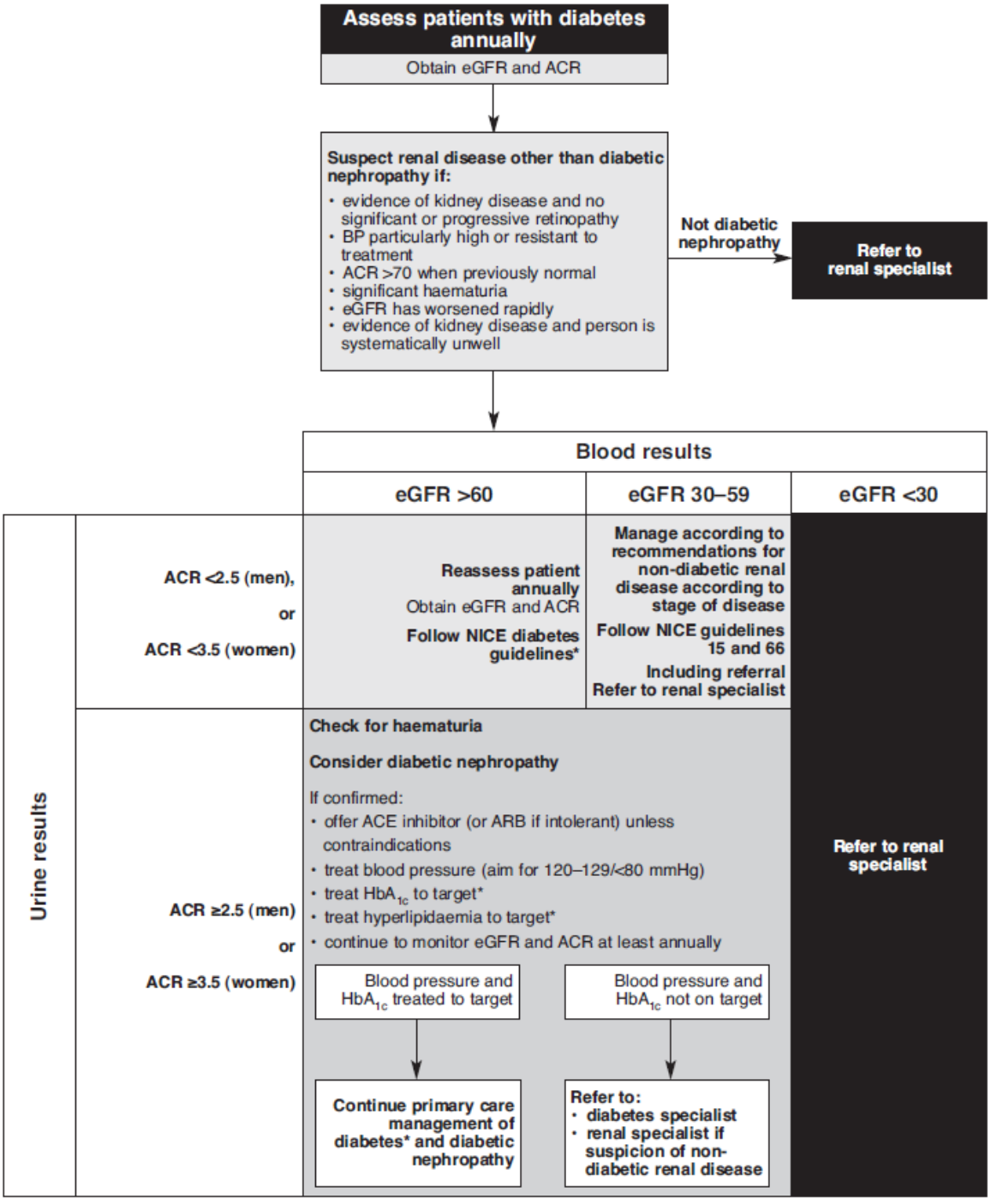


Figure 3.1 Investigations and interventions at different stages of CKD. This algorithm should be used as an aide memoire in primary care to trigger various investigations and interventions relevant for people in different stages of CKD. Stages of CKD are shown from left to right and activities appear as horizontal bands, some of which are more relevant to early or late disease, as indicated by their positioning and by the graded shading. BP = blood pressure; NSAID = non-steroidal anti-inflammatory drug; PTH = parathyroid hormone.



*See pages 33 and 147 for management of isolated invisible haematuria.

Figure 3.2 Identification, diagnosis and referral of patients with CKD but without diabetes. eGFR is expressed as ml/min/1.73m^2. Albumin:creatinine ratio (ACR) and protein:creatinine ratio (PCR) are expressed as mg/mmol.



*See NICE clinical guidelines on type 1 diabetes (http//:www.nice.org.uk/CG15) and type 2 diabetes (http//:www.nice.org.uk/CG66).

Figure 3.3 Diagnosis and referral of patients with CKD and diabetes. eGFR is expressed as ml/min/1.73m^2. Albumin:creatinine ratio (ACR) is expressed as mg/mmol.

P.4 Section 4: Investigation of CKD

P.4.1 Section 4.1: Measurement of kidney function

P.4.1.1 Section 4.1.1: Clinical introduction

The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons and is the best index of overall kidney function. Knowledge of GFR is essential for the diagnosis and management of CKD and is a translatable concept. Because a normal GFR is roughly 100 ml/min/1.73m^2, we can explain kidney function to patients and carers in terms of a percentage of normal – a more easily understandable concept than GFR.

The gold standard methods of estimating GFR require measurement of an ideal filtration marker. These markers should be freely filtered by the glomerulus, should not be bound to plasma proteins, must be excreted unchanged and not be subject to either tubular secretion or absorption. Commonly used markers include inulin, 51Cr-EDTA, 125I-iothalamate and iohexol. Gold standard methods of assessing GFR are technically demanding, expensive, time consuming and unsuitable for widespread identification of CKD in the 'at risk' population.

At the other end of the accuracy scale lies measurement of serum creatinine, which is a universally available endogenous test of kidney function. Although easy and cheap to measure, creatinine is subject to non-renal and analytical influences which make it insufficiently sensitive to detect moderate CKD on its own. Measurement of 24-hour urinary creatinine clearance improves the accuracy but is also subject to the same non-renal and analytical influences compounded by inaccuracies in urine collection, to say nothing of the inconvenience associated with 24-hour urine collections. An alternative and more accurate endogenous marker is cystatin C, a 13 kDa cationic protein produced by all nucleated cells. Serum cystatin C levels are chiefly determined by GFR. Potential limitations of cystatin C as a marker of GFR include lack of assay standardisation, the requirement for a dedicated analytical system, and increased costs relative to serum creatinine (approximately £3/assay compared to <£0.10/assay).

A further alternative is to measure serum creatinine and estimate GFR using an equation which corrects for some of the more significant non-renal influences. This approach is known to be more sensitive for the detection of CKD than serum creatinine and more accurate than creatinine clearance.

So what have previous guideline groups recommended? The SIGN guidelines[620] recommended use of prediction equations in place of 24-hour creatinine clearance or serum creatinine alone and preferred prediction equations to cystatin C on the grounds of practical and resource considerations. The Modification of Diet in Renal Disease (MDRD) equation was preferred to the Cockcroft-Gault formula. The UK CKD guidelines and the UK consensus conference recommended use of the 4-variable MDRD equation using zero biased creatinine methods.[39,662] Others (KDOQI, CARI and KDIGO)[5,105,376,482] have recommended that serum creatinine should not be used alone to assess kidney function, that creatinine assays should be traceable to a reference creatinine method, and that an estimated GFR should be reported by laboratories alongside the serum creatinine measurement using the 4-variable MDRD equation.

What is the best diagnostic test to measure renal function in routine clinical practice?

P.4.1.2 Section 4.1.2: Methodology

Due to the large volume of studies in this area, studies were included if the sample size was greater than 100, gold standard tests were used as the reference test, and bias, accuracy, sensitivity, specificity, positive and negative predictive values, test correlation, or diagnostic accuracy (area under the receiver–operator curve (ROC)) outcomes were reported. For studies comparing the MDRD predictive equation with other equations, the serum creatinine measurements had to be calibrated to the MDRD laboratory reference standard. Two exceptions to the sample size cut-off were the studies that evaluated the GFR equations in older people.[100,367] Publications that reported on the accuracy of tests in dialysis or renal replacement patients were excluded.

Five studies[77,121,250,254,276] that evaluated the accuracy of serum cystatin C were rejected because gold standard tests were not used as the comparator or because creatinine (the MDRD equation) was not calibrated properly to the MDRD laboratory reference values.

Nine studies[88,100,250,276,367,409,570,571,646] that evaluated the accuracies of predictive equations in estimating GFR were rejected due to methodological limitations or because the serum creatinine measurements were not calibrated to the MDRD assay as determined by isotope-dilution mass spectrometry.

Five studies[215,241,289,377,549] assessing the accuracies of the MDRD equation and the Cockcroft-Gault equation in predicting the glomerular filtration rate were included. These were conducted in large sample sizes (N=219 to 2095) and were quite heterogeneous in terms of the population studied: older populations, diabetic nephropathy, mild renal impairment, moderate renal impairment, or healthy populations. Differences in performances of the equations may be explained by the different populations in which the equations were derived, and multiple sources of measurement variation when measuring creatinine.

P.4.1.3 Section 4.1.3: Health economics methodology

No health economics papers were found to review.

The estimated reagent costs for some of the tests were presented to the GDG. Cystatin C was the most expensive followed by the creatinine-based technology. However these costs do not take into account all overheads. Furthermore, there are economies of scale if reagents are used in large quantities.

P.4.1.4 Section 4.1.4: Evidence statements

Cystatin C concentration versus predictive equations (MDRD or Cockcroft-Gault)

Two cross-sectional studies[250,276] that compared cystatin C to the MDRD and Cockcroft-Gault equations were rejected because the serum creatinine measurements were not calibrated to the MDRD assay.

Comparisons of predictive equations for estimating GFR

Five studies compared the performances of the Cockcroft-Gault and the MDRD equations in predicting GFR. The values of several diagnostic parameters are summarised in Table 207.

Table 207: Summary of predictive equations to estimate renal function

Study	Evidence level	N	Bias (ml/min /1.73m^2)	Sensitivity (%)	Specificity (%)	Accuracy (P30)	Test correlation with gold standard
[215]	1b +	2095 (CKD + kidney donors)	MDRD –0.99 ml/min/ 1.73m^2, p=0.001 CG 1.94 ml/min/ 1.73m^2, p<0.0001 Bias was greater for MDRD equation (–6.2 ml/min/1.73m^2) than the Cockcroft-Gault equation (–0.3 ml/min/1.73m^2) in patients with a measured GFR > 90 ml/min/1.73m^2. The MDRD equation was less biased than the Cockcroft-Gault equation in patients with stage 3, 4, or 5 CKD. The MDRD	MDRD (78.9%), CG (67.6%) in stage 4 CKD MDRD (64.8%) CG (43%) in stage 5 CKD	Both MDRD and Cockcroft-Gault equations had similar specificities across the 5 stages of CKD (approx. 90%).	MDRD 92% CG 88% in people with GFR > 60 ml/min/1.73m^2 People with GFR <60 ml/min/1.73m^2 (82% MDRD versus 69% Cockcroft-Gault).	MDRD (r=0.910) Cockcroft-Gault (r=0.894)

Study	Evidence level	N	Bias (ml/min /1.73m^2)	Sensitivity (%)	Specificity (%)	Accuracy (P30)	Test correlation with gold standard
			equation was significantly less biased than the Cockcroft-Gault equation when patients were analysed by age (above or below 65 years) and gender (p<0.0001).				
[241]	1b +	219 (CKD + non-CKD)	MDRD 2275 arbitrary units vs.CG 630 arbitrary units	NR	NR	MDRD 62% vs.CG 48.8%, p <0.01	NR
[289]	II +	1286 (type 1 diabetes)	MDRD – 22 vs.CG –6	NR	NR	When GFR >120 MDRD 97% CG 87%, p <0.001 When GFR <120 MDRD 82% CG 92%, p <0.001	NR
[377]	1b +	1628 (CKD)	MDRD 0.2 vs.CG –7.3 When GFR >90 MDRD –3.0 vs.CG –21.8	MDRD 97 vs.CG 85, p<0.001	MDRD 70 vs.CG 88, p<0.001	MDRD 90% (95% CI 89–91) vs.CG 60% (95% CI 58–62)	NR
[549]	1b +	828 (CKD) 457 (kidney donor)	MDRD –0.5 vs.CG 3.5, p < 0.001	NR	NR	MDRD 71% CG 60%, p <0.001	CKD group: MDRD (r=0.90) and CG (r=0.89). Kidney donor control group:

Study	Evidence level	N	Bias (ml/min /1.73m^2)	Sensitivity (%)	Specificity (%)	Accuracy (P30)	Test correlation with gold standard
							MDRD (r=0.36) CG (r=0.41)

NR= not reported

Test correlation

Regression analysis was used to determine the correlation between GFR measured by the gold standard test and GFR calculated using the MDRD or Cockcroft-Gault predictive equations. Two studies[215,549] showed that both the MDRD and Cockcroft-Gault equations correlated highly with the measured GFR in people with CKD, often with no statistical difference between the correlation coefficients for the MDRD and Cockcroft-Gault equations. Both MDRD and Cockcroft-Gault equations correlated poorly with the gold standard test in renal donors. [549] (Level 1b +)

Bias

In diabetic populations[289] and in CKD populations, [241,549] the MDRD equation often under-estimated the measured GFR. The Cockcroft-Gault equation often overestimated the GFR. (Level 1b +)

In CKD populations, the MDRD equation was superior to the Cockcroft-Gault equation in terms of bias.[215,377,549] The MDRD equation slightly underestimated the measured GFR, while the Cockcroft–Gault equation significantly overestimated the GFR (–0.5 vs. 3.5 ml/min/1.73m^2, p < 0.001). The MDRD equation was also significantly less biased than the Cockcroft-Gault equation in the nondiabetic CKD (N=579) subgroup, the diabetic CKD (N=249) subgroup, and in people with a measured GFR <30 ml/min/1.73m^2 (N=546) (p <0.001 in each group). (Level 1b +)

The MDRD and Cockcroft-Gault equations were significantly more biased in people with GFR >60 ml/min/1.73m^2 (N=117). The MDRD equation underestimated the measured GFR, while the Cockcroft-Gault equation significantly overestimated the GFR (–3.5 vs. 7.9 ml/min/1.73m^2, p <0.001). In the kidney donor control group (N=459), the Cockcroft-Gault equation was superior to the MDRD equation in terms of bias (1.9 vs. –9.0 ml/min/1.73m^2, p <0.001).[549] (Level 1b+)

Sensitivity and specificity

Two studies[215,377] reported sensitivity and specificity outcomes for the MDRD and Cockcroft-Gault equations. The MDRD had higher sensitivity than the Cockcroft-Gault equation. Specificity was similar for the two predictive equations. (Level 1b+)

Accuracy (P30)

Five studies[215,241,289,377,549] reported the percentage of estimated GFR values falling within 30% of the GFR values measured by the gold standard test. Generally, the MDRD equation was more accurate than the Cockcroft-Gault equation. (Level 1b+)

Area under the ROC

Area under the ROC values is a measure of the overall diagnostic accuracy or power of a test. The MDRD equation had significantly higher diagnostic accuracy (AUC=0.961) than the Cockcroft-Gault equation (AUC=0.942, p <0.01). [377] (Level 1b+)

P.4.1.5 Section 4.1.5: From evidence to recommendations

The evidence suggests that in general the 4-variable MDRD performs better than the Cockcroft-Gault equation. However, in older people and in people with GFR greater than 60ml/min/1.73m^2 the MDRD is subject to bias and can underestimate GFR.

The GDG noted that serum creatinine is correlated with muscle mass and therefore estimation of GFR using prediction equations in people with extremes of muscle mass is subject to inaccuracy. In those with increased muscle mass GFR will be under estimated and in those with reduced muscle mass GFR will be over estimated.

Gold standard measures of GFR are time consuming and expensive to perform but where a highly accurate measurement of GFR is required, for example in assessment of kidney donors or for accurate calculation of dosing of potentially toxic chemotherapy, the evidence suggests that GFR estimated from prediction equations is insufficiently accurate.

The GDG agreed that significant changes in GFR are equally important in those individuals with GFR greater than 60 ml/min/1.73m^2. Where laboratories do not report levels of GFR greater than 60 ml/min/1.73m^2 the GDG considered that a rise in serum creatinine of greater than 20% should be considered significant.

Although the original MDRD equation included a correction factor for the American black population, there are no correction factors for other populations and in routine use the derived GFR is not corrected for any ethnicity other than African-Caribbean.

Although most laboratories would be capable of measuring cystatin C concentrations there is no evidence to suggest that it was more useful than using the MDRD, with the caveat that existing evidence comparing cystatin C and the MDRD failed to appropriately calibrate serum creatinine measurements to the method of the MDRD laboratory. Cystatin C measurement is also currently more expensive.

P.4.1.6 Section 4.1.6: RECOMMENDATIONS

R1 Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of GFR (eGFR) using a prediction equation (see recommendation R2) in addition to reporting the serum creatinine result.[f]

R2 Use the isotope dilution mass spectrometry (IDMS)-traceable simplified MDRD equation to estimate GFR, using creatinine assays with calibration traceable to a standardised reference material.

[f] eGFR may be less reliable in certain situations (for example, acute renal failure, pregnancy, oedematous states, muscle wasting disorders, amputees and malnourished people) and has not been well validated in certain ethnic groups (for example, Asians and Chinese).

Ideally use creatinine assays that are specific and zero-biased compared to IDMS (e.g. enzymatic assays). When non-specific assays are used (e.g. Jaffe assays), employ appropriate assay-specific adjustment factors to minimise between-laboratory variation (e.g. those provided by national external quality assessment schemes).

R3 Where indicated, apply a correction factor for ethnicity to reported GFR values (multiply eGFR by 1.21 for African-Caribbean ethnicity).[g]

R4 Interpret reported values of eGFR ≥60 ml/min/1.73m^2 with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases.

R5 Where eGFR is simply reported as ≥60 ml/min/1.73m^2, use a rise in serum creatinine concentration of >20% to infer significant reduction in renal function.

R6 Where a highly accurate measure of GFR is required (e.g. during monitoring of chemotherapy and in the evaluation of renal function in potential living donors), consider a gold standard measure (inulin, 51Cr-EDTA, 125I-iothalamate or iohexol).

R7 In cases where there are extremes of muscle mass (e.g. body builders, amputees, muscle wasting disorders) interpret the eGFR with caution. (Reduced muscle mass will lead to over-estimation and increased muscle mass to under-estimation).

P.4.2 Section 4.2 - Factors affecting the biological and analytical variability of GFR estimated from measurement of serum creatinine

P.4.2.1 Section 4.2.6: RECOMMENDATIONS

R8 Advise people not to eat any meat in the 12 hours before having a blood test for GFR estimation. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture.

R9 An eGFR result below 60 ml/min/1.73m^2 in a person not previously tested should be confirmed by repeating the test within 2 weeks. Make an allowance for biological and analytical variability of serum creatinine (±5%) when interpreting changes in eGFR.

P.4.3 Section 4.3 Detection of blood and protein in the urine

P.4.3.1 Section 4.3.3: Methodology

ACR and PCR have been shown to correlate with the 24-hour albumin or protein excretion rate. Proteinuria is defined as a 24-hour protein excretion rate ≥150 mg/24 h. Microalbuminuria is defined as a 24-hour albumin excretion rate of 30-300 mg/24 h. Macroalbuminuria is defined as a 24-hour albumin excretion rate of >300 mg/24 h. In these assays, albumin is measured with immunonephelometric methods. Protein is measured in turbidometric assays with Bradford reagents, benzethonium chloride, or pyrogallol red-molybdate.

[g] In practice this correction factor should also be applied to those of African ethnicity.

P.4.3.2 Section 4.3.6: RECOMMENDATIONS

Haematuria

R10 When testing for the presence of haematuria, use reagent strips rather than urine microscopy.

- Evaluate further if there is a result of 1+ or more.
- Do not use urine microscopy to confirm a positive result.

Proteinuria

R11 Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR .

R12 To detect and identify proteinuria, use urine albumin:creatinine ratio (ACR) in preference, as it has greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria. For quantification and monitoring of proteinuria, PCR can be used as an alternative. ACR is the recommended method for people with diabetes.

R13 For the initial detection of proteinuria, if the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5g/24 h or more) and less than 70 mg/mmol (approximately equivalent to PCR less than 100 mg/mmol, or urinary protein excretion less than 1 g/24 h) this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, or the PCR 100 mg/mmol or more, a repeat sample need not be tested.

P.4.4 Section 4.4: Urinary albumin: creatinine and protein: creatinine ratios, and their relationship to 24-hour urinary protein

P.4.4.1 Section 4.4.1: Clinical introduction

Proteins normally excreted in the urine include albumin, low molecular weight immunoglobulin (filtered plasma proteins), and secreted tubular proteins. There is no consistent definition of proteinuria. The upper limit of normal excretion is approximately 150 mg/24 h, equivalent to a protein:creatinine ratio (PCR) of 15 mg/mmol (given an average daily urine creatinine excretion of 10 mmol), but the cut off for abnormal varies from laboratory to laboratory. By contrast, urinary albumin measurement provides a quantitative, relatively standardised measurement of excretion of the single most important protein in most nephropathies. The normal mean value for urine albumin excretion is 10 mg/day, microalbuminuria is defined as 30-300 mg/day or an albumin:creatinine ratio (ACR) of >2.5 mg/mmol in men and >3.5 mg/mmol in women. Macroalbuminuria is a urinary albumin excretion greater than 300 mg/day (ACR >30 mg/mmol).

Protein excretion displays considerable biological variability, and may be increased by urinary tract infection (UTI), upright posture, exercise, fever, and heart failure as well as by kidney disease. Biological variation of both measures is high, with lower variation generally being reported for an albumin:creatinine ratio (ACR) on an early morning urine (EMU) compared to PCR (e.g. 36% versus 48% respectively). There is a high correlation between total protein and albuminuria at high levels of protein excretion (so-called nephrotic range proteinuria, PCR >300 mg/mmol) but at low levels

correlation is poor. This is because urine protein measurement in the normal range and at low levels is both imprecise and relatively non-specific. Albumin as a proportion of total protein is highly variable at normal and moderately increased levels of proteinuria.[55,174,555,630]

The UK CKD Guidelines have defined proteinuria as a PCR of ≥45 mg/mmol or an ACR ≥30 mg/mmol but suggest that, in the absence of concomitant haematuria, this should not act as a trigger for active intervention until the PCR exceeds 100 mg/mmol (ACR >70 mg/mmol).[662] KDOQI guidelines define proteinuria as a PCR >23 mg/mmol (200 mg/g). The Welsh Renal NSF has defined proteinuria as a PCR of ≥100 mg/mmol, approximately equivalent to an excretion rate of 1000 mg/24 h.

In the most common types of CKD (i.e. that due to diabetes, hypertension and glomerular disease) and in kidney transplant recipients, albumin is both the most abundant protein in urine and a more sensitive marker of disease. The NKF-KDOQI guidelines therefore recommend urinary albumin measurement in preference to total protein when detecting and monitoring proteinuria. Conversely, the UK CKD guidelines and CARI guidelines have recommended urine PCR for non-diabetic kidney disease, with ACR being reserved for patients with diabetes.[662] The Welsh Renal NSF has adopted a similar position and this was endorsed by the UK consensus conference statement and by the Scottish Intercollegiate Guidelines Network.[39]

P.4.4.2 Section 4.4.2: Methodology

Call for evidence: methodology

The unpublished manuscript by MacGregor et al. detailed a retrospective analysis of 6761 urine samples. Given that this manuscript was shared with the GDG as unpublished work in progress, there are some methodological limitations. The correlation between ACR (immunoturbidometric assay) and PCR (pyrogallol red or subsequently a benzethonium turbidometric assay) was assessed. The relationships between 24-h protein excretion and ACR or PCR were also analysed in a non-randomised subgroup for whom 24-hour protein had been collected (N=1739). Areas under the receiver-operator curves were determined, along with the thresholds of both ACR and PCR to detect a 24-hour protein excretion rate >1 g/day or >450 mg/day with sensitivity of 0.95.[403]

P.4.4.3 Section 4.4.7: RECOMMENDATIONS

R14 In people without diabetes consider clinically significant proteinuria to be present when the ACR is 30 mg/mmol or more (this is approximately equivalent to a PCR 50 mg/mmol or more, or urinary protein excretion 0.5 g/24 h or more).

R15 In people with diabetes consider microalbuminuria (ACR more than 2.5 mg/mmol in men and ACR more than 3.5 mg/mmol in women) to be clinically significant.

R16 All people with diabetes, and people without diabetes with a GFR less than 60 ml/min/1.73m^2, should have their urinary albumin/protein excretion quantified. The first abnormal result should be confirmed on an early morning sample (if not previously obtained).

R17 Quantify by laboratory testing the urinary albumin/protein excretion of people with an eGFR less than 60 ml/min/1.73m^2 if there is a strong suspicion of CKD (see also 4.2.7).

P.4.5 Section 4.5: Indications for renal ultrasound in the evaluation of CKD

P.4.5.1 Section 4.5.6: RECOMMENDATIONS

R18 Offer a renal ultrasound to all people with CKD who:

- have progressive CKD (eGFR decline >5 ml/min/1.73m^2 within one year or >10 ml/min/1.73m^2 within 5 years)
- have visible or persistent invisible haematuria
- have symptoms of urinary tract obstruction
- have a family history of polycystic kidney disease and are aged over 20
- have stage 4 or 5 CKD
- are considered by a nephrologist to require a renal biopsy.

R19 Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them.

P.5 Section 5: Classification and early identification

P.5.1 Section 5.1: The influence of GFR, age, gender, ethnicity and proteinuria on patient outcomes

P.5.1.1 Section 5.1.1: Clinical introduction

If we cannot prevent CKD then we want to minimise the associated adverse outcomes. To do this we need to know:

- what the adverse outcomes are
- at what level of GFR we should be alert to adverse outcomes and
- the impact of associated factors such as age, gender and presence or absence of proteinuria at any given level of GFR.

Large population studies have clearly suggested that the risk of death, hospitalisation and cardiovascular events rises exponentially at levels of GFR below 60 ml/min/1.73m^2.[229] Other complications associated with reduced GFR, such as the increased potential for dose-related drug toxicity, are less obvious but equally important.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) stratified chronic kidney disease into five stages according to glomerular filtration rate and the presence of kidney damage:

- Stage 1: GFR >90 ml/min/1.73m^2 with other evidence of kidney damage (persistent microalbuminuria, persistent proteinuria, persistent haematuria, structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, or biopsy-proven chronic glomerulonephritis)
- Stage 2: GFR 60–89 ml/min/1.73m^2 with other evidence of kidney damage
- Stage 3: GFR 30–59 ml/min/1.73m^2
- Stage 4: GFR 15–29 ml/min/1.73m^2

- Stage 5: GFR <15 ml/min/1.73m^2.

CKD is common and its prevalence increases markedly with age, with a female predominance. However, the CKD classification is neither staged according to age and gender, nor according to level of proteinuria. All patients, regardless of age, gender and proteinuria or albuminuria are considered to have at least moderately severe CKD when their GFR is <60 ml/min/1.73m^2. However, we have some evidence that GFR reduces as a consequence of ageing,[390] although the exact level of reduction is still a subject of debate, and reduced GFR is very common in certain older populations.[221] It has been suggested that the rate of progression of CKD in black and minority ethnic groups may be higher than in Caucasians.24 The ABLE projects in the UK have also suggested that kidney disease in people of South Asian and African-Caribbean ethnicity may deteriorate more rapidly to established renal failure.[340] Long term, the ABLE study aims to identify the reasons for this faster deterioration.

The degree of proteinuria is a significant risk factor both for progression of CKD and for cardiovascular disease.[40,267,301,345] We therefore need a better understanding of the prognostic significance of different levels of GFR, and of what other factors should be considered. Intuitively a 'one size fits all' approach to clinical decision making throughout the population is unlikely to be appropriate. This has already been recognised by the CARI (Caring for Australasians with Renal Impairment) guidelines which recommend that the suffix '(p)' should be applied to the corresponding CKD stage for all patients with proteinuria ≥1 g/day. The recently published SIGN (Scottish Intercollegiate Guidelines Network) guideline also makes the same recommendation, as did the UK consensus conference on early CKD which also recommended sub-classifying CKD stage 3 into 2 groups: 3A which defines a lower risk group with GFR 45–59 ml/min/1.73m^2, and 3B which defines a higher risk group with GFR 30–44 ml/min/1.73m^2.[39]

At what level of GFR are patient outcomes significantly affected? Does this change with age? Gender? Ethnicity? Presence or absence of proteinuria?

P.5.1.2 Section 5.1.2: Methodology

Twenty-two longitudinal studies assessed the risks of all-cause mortality, cardiovascular disease, hospitalisation, renal disease progression, and the quality of life of adults with decreasing eGFR levels. Baseline characteristics were significantly different between groups with lower eGFR compared with higher eGFR. People with low eGFR were almost always older, more likely to be female, and had higher prevalence of diabetes and cardiovascular diseases. While statistical analyses in these studies have been adjusted for confounding variables such as age, gender, race, and several comorbidities, it is difficult to identify all variables which could potentially affect the size of the risk. These unknown variables make it impossible to assign cause and effect, and the confidence intervals were sometimes so wide that the associations with eGFR could be spurious.

Eight cohort studies examined the association between different eGFR levels and several outcomes of interest in populations with concomitant cardiovascular disease; specifically high-risk hypertension,[561] acute myocardial infarction,[677,726] heart failure,[268] acute coronary syndrome,[336] coronary disease,[62] coronary artery disease[361] and peripheral arterial disease.[499] These studies ranged in sample size from 1015 to 31,897 and length of follow-up ranged from 1 to 6 years. The mean age of people with higher eGFR (typically >60 ml/min/1.73m^2) ranged from 57 to 72 years, while the mean age range of those with lower eGFR (typically <60 ml/min/1.73m^2) ranged from 62 to 83 years.

The study by Beddhu et al.was rejected due to missing patient baseline data, and lack of inclusion and exclusion criteria.

A very large US cohort study (N=1,120,295, follow-up 2.8 years, age range 47–71) examined age-adjusted risk of mortality, cardiovascular events, and hospitalisation in people with stage 3, 4, or 5 CKD compared to people with GFR >60 ml/min/1.73m^2.[229] In another US cohort study, participants with CKD were age and sex matched with people without CKD (N=19,945 pairs, follow-up 4.5 years) and the risk of all-cause mortality was examined.[239] The KEEP study assessed mortality and cardiovascular disease (N=37,153, median follow-up 16 months) in a self-selected population of people with diabetes, hypertension, or a family history of kidney disease, hypertension, or diabetes.[438] Participants in the ARIC cohort (N=14,280) were assessed for incidence of peripheral arterial disease as a function of eGFR.[714]

A UK cohort study (N=3249 unreferred, 2.6 years follow-up, mean age 82 years) examined the mortality outcomes of people who had not been referred to renal services with stage 4 or 5 CKD compared to eGFR 30–42 ml/min/1.73m^2.[319]

Three cohort studies in diabetic adults examined the association of eGFR with renal disease progression and cardiovascular outcomes.[464,534,640] A UK study of people identified from a diabetes register (N=3288, median follow-up 10.5 years) assessed all-cause mortality and mortality due to circulatory disease, ischaemic heart disease, or cerebrovascular disease in this population stratified by eGFR.[464] The Patel et al. study (N=12,570, follow-up 3 years, range of groups' mean ages 64–72) reported mortality rates and kidney disease progression rates at different eGFR levels in a predominantly male diabetic cohort. This study was rejected as there was little statistical analysis of the results; only mortality rates were presented.

Quality of life outcomes such as cognitive impairment, frailty, and disability were assessed in postmenopausal women[361] or in older populations with varying levels of serum creatinine132 or eGFR.[360]

The effect of proteinuria or no proteinuria at a particular eGFR on the risk of ESRD was assessed in a Japanese population study (N=95,255, follow-up 7 years).[303] The So et al. study investigated the effect of proteinuria on patient outcomes within several GFR ranges in a Chinese diabetic cohort (N=4421, follow-up 3.3 years, mean ages in higher versus lower eGFR ranges 57 and 69 years).

The effects of age and gender on mortality and kidney disease progression were examined in people with stage 3 CKD in a Norwegian population study (N=3027, median observation time 3.7 years, median age 75 years).[186] In a predominantly male cohort study (N=8,218,817, mean follow-up 3.17 years), people were stratified by age within decreasing ranges of eGFR and the effect of age on mortality was examined.[498] In another analysis of this cohort (N=209,622, follow-up 4 years), people were stratified by eGFR and the risk of death or progression to ESRD was assessed with increasing age.[500]

There were no studies that assessed cardiovascular and renal outcomes as a function of race within different levels of renal function.

Table 208 summarises the association of GFR and mortality, cardiovascular risk, and renal disease progression in adults with varying severity of CKD.

P.5.1.3 Section 5.1.3: Health economics methodology

There were no health economics papers to review.

P.5.1.4 Section 5.1.4: Evidence statements

All-cause mortality

Three studies showed that the risk of all-cause mortality rose sharply in people with eGFR <45 ml/min/1.73m^2.[229,268,677] Every 10 ml/min/1.73m^2 decrease in GFR from 75 ml/min/1.73m^2 was associated with a significantly higher risk of all-cause mortality (adjusted HR 1.09, 95% CI 1.06–1.14, p <0.001).[268] (Level 2+)

Cardiovascular mortality

Three studies showed that risk of cardiovascular mortality increased with declining renal function.[268,464,677] The risk of circulatory disease mortality, ischaemic heart disease mortality, and cerebrovascular disease mortality all significantly increased with decreasing renal function.[464] (Level 2+)

Cardiovascular events

Three studies showed NS risk of cardiovascular events in people with GFR 60–89 ml/min/1.73m^2 compared with eGFR >90 ml/min/1.73m^2.[438,640,677] The risk of cardiovascular events significantly increased at eGFR <60 ml/min/1.73m^2.[438,561,677,714] The risk of cardiovascular events rose sharply in people with eGFR <45 ml/min/1.73m^2.[229] (Level 2+)

Frailty

People with chronic renal insufficiency (CRI) (N=648) had a significantly increased risk of frailty (adjusted odds ratio (OR) 1.76, 95% CI 1.28–2.41, p not stated) compared to people without CRI. The prevalence of frailty increased with decreasing GFR (p for trend <0.001) and was particularly high in those with GFR <40 ml/min/1.73m^2. Black ethnicity and female gender were associated with increased likelihood of frailty.[631] (Level 3)

Disability

There was NS risk of disability for people with CRI compared to people without CRI. Black race and female gender were associated with increased likelihood of disability.[631] (Level 3)

Cognitive impairment (3MS score <80)

The risk of cognitive impairment was significantly greater for people with eGFR 45–59 ml/min/1.73m^2 (adjusted OR 1.32, 95% CI 1.03–1.69) or eGFR <45 ml/min/1.73m^2 (adjusted OR 2.43, 95% CI 1.38–4.29, compared to people with GFR >60 ml/min/1.73m^2).[360] (Level 2+)

In postmenopausal women under 80 years old with established coronary artery disease, the risk of cognitive impairment was significantly higher at eGFR <30 ml/min/1.73m^2 compared to women with eGFR >60ml/min/1.73m^2 (adjusted OR 5.01, 95% CI 1.27–19.7). There was NS risk of cognitive

impairment at eGFR 45–49 or 30–44 ml/min/1.73m^2. A decline in eGFR of 10 ml/min/1.73m^2/year was associated with an increased risk of cognitive impairment (adjusted OR 1.27, 95% CI 1.01–1.59).[361] (Level 3)

Effect of age on all-cause mortality

When participants with various levels of CKD were age- and sex-matched with people without CKD (N=19,945 pairs, follow-up 4.5 years), the relative risk (RR) of mortality in people aged 60, 75 or 90 was relatively stable until eGFR decreased to 55 ml/min/1.73m^2 when the risk of mortality increased in all three age groups (<60, 75 or 90 years). The risk of mortality was highest in those <60 years old. At eGFR <30 ml/min/1.73m^2, the mortality risk increased sharply. Again the risk was highest in those <60 years of age.[239] (Level 2+)

The risk of all-cause mortality at a certain eGFR decreased as age increased. An eGFR of 50–59ml/min/1.73m² was still associated with an increased risk of death among all age groups under 65 years.[498] (Level 3)

However, in a Norwegian cohort of people with stage 3 CKD stratified by age (≤69 years, 70–79 years, >79 years) each 10-year increment of age was associated with a significantly increased risk of all-cause mortality (HR 2.28, 95% CI 2.11–2.46, p <0.0001).[186] The risk of death increased with increasing age within each stratum of baseline eGFR.[500] (Level 3)

Effect of age on renal failure

In people with stage 3 CKD, each 10-year increment of age was associated with a significantly decreased risk of renal failure (HR 0.75, 95% CI 0.63–0.89, p=0.0009).[186] The risk of ESRD decreased with increasing age within each stratum of baseline eGFR.[500] (Level 3)

Effect of age on GFR decline

Each 10-year increment in age was associated with a decline in GFR (–0.38 ml/min/1.73m^2/year, 95% CI –0.51 to –0.26, p <0.0001).[186] (Level 3)

Effect of gender on all-cause mortality

In people with CKD and acute coronary syndromes, men had a significantly increased risk of all-cause mortality compared to women (HR 1.185, 95% CI 1.116–1.259, p not stated.[336] (Level 2+)

Women with stage 3 CKD had a significantly reduced risk of all-cause mortality compared with men with stage 3 CKD (HR 0.55, 95% CI 0.48–0.62, p <0.0001).[186] (Level 3)

Unreferred women had a decreased risk of all-cause mortality compared to unreferred men (HR 0.73, 95% CI 0.65–0.82, p <0.001).[319] (Level 3)

Compared to males, females had a decreased risk of in-hospital death (adjusted OR 0.7, 95% CI 0.5–1.5, p=0.012).[726] (Level 2+)

Effect of gender on renal failure

Women with stage 3 CKD had a significantly reduced risk of renal failure compared with men with stage 3 CKD (HR 0.35, 95% CI 0.21–0.59, p<0.0001).[186] (Level 3)

Effect of gender on GFR decline

The decline in eGFR in men with stage 3 CKD was greater (–1.39 ml/min/1.73m^2 /year) than in women (–0.88 ml/min/1.73m^2/year). Female gender was associated with an increased change in eGFR compared to men (+0.50 ml/min/1.73m^2 /year, 95% CI 0.20–0.81) p=0.001).[186] (Level 3)

Effect of proteinuria on all-cause mortality

The risk of death increased as eGFR decreased and proteinuria was present. In an age and sex matched cohort, the matched risk ratio was 2.09 (95% CI 1.71–2.55) for people with proteinuria and eGFR 60–89 ml/min/1.73m^2. For people with proteinuria and eGFR 30–59 ml/min/1.73m^2, the matched risk ratio was 2.73, 95% CI 2.23–3.35. For people with proteinuria and eGFR 15–29 ml/min/1.73m^2, the matched risk ratio was 6.96 (95% CI 4.63–10.46).[239] (Level 2+)

Effect of proteinuria on cardiovascular events (ischemic heart disease, stroke, congestive heart failure, revascularisation procedures)

At a given eGFR, the presence of proteinuria significantly increased the risk of cardiovascular events.[438,640] When eGFR was ≥90 ml/min/1.73m^2, those with albuminuria had a significantly increased risk of cardiovascular events than those without albuminuria (HR 1.85, 95% CI 1.07–3.18, p=0.03). Similarly, people with GFR 60–89 ml/min/1.73m^2 with albuminuria had a significantly increased risk of cardiovascular events than those without albuminuria (HR 1.89, 95% CI 1.13–3.16, p=0.016).[640] (Level: 2+ and 3)

Effect of proteinuria on ESRD

In a Japanese cohort study, proteinuria significantly increased the risk of ESRD (HR 4.19, 95% CI 3.76–4.68, p<0.0001). For people with proteinuria and creatinine clearance (CrCl) 64.0–79.3 ml/min (N=727), the 7-year cumulative incidence of ESRD per 1000 subjects was 8.3, whereas it was only 0.04 in those without proteinuria (N=22,420). For people with proteinuria and CrCl 50.2–63.0 ml/min (N=807), the 7-year cumulative incidence of ESRD per 1000 subjects was 13.6, whereas it was only 0.7 in those without proteinuria (N=22,232). For people with proteinuria and CrCl <50.2 ml/min (N=1198), the 7-year cumulative incidence of ESRD per 1000 subjects was 86.8, whereas it was only 1.2 in those without proteinuria (N=21,878).[303] (Level 2+)

Table 208: Association of adverse outcomes with declining GFR

Reference	Population	Reference GFR (ml/min/ 1.73m^2)	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
Outcome: risk of all-cause mortality								
[499]	Men with	≥ 60	-	-	1.32 (1.13, 1.53)		2.97 (2.39, 3.69)	

Reference	Population	Reference GFR (ml/min/ 1.73m^2)	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
	peripheral vascular disease (N=5787)							
268	Heart failure (N=2680)	> 90	NS	NS	1.50 (1.12, 2.00), p=0.006	1.91 (1.42, 2.58), p<0.001		
336	Acute coronary syndrome (N=5549)	> 80	0.889 (0.795, 0.994) –decreased risk		1.060 (1.008, 1.115)		1.225 (1.175, 1.292)	
677	Acute MI and LVEF ≤ 40% (N=2183)	≥ 75	-	NS	NS	1.81 (1.32, 2.48),		
640	Type 2 diabetes (N=4421)	≥ 90	NS		2.34 (1.16, 4.70)		9.82 (4.53, 21.0)	-
229	Kaiser Permanente cohort (N= 1120295)	≥ 60	-	-	1.2 (1.1, 1.2)	1.8 (1.7-1.9)	3.2 (3.1-3.4)	5.9 (5.4-6.5)
239	Kaiser Permanente cohort (N=19945 sex, age matched pairs)	60-89	-	-	matched RR 1.311 (1.142, 1.505), p<0.0001		matched RR 3.335 (2.272, 4.896), p<0.0001	
319	People unreferred to renal services (N=3822)	30-42.8	-	-	-	-	1.41 (1.25, 1.60), p <0.001	3.12 (2.53, 3.83), p <0.001
438	Adults with DM, HYP, or family history of DM, HYP, or kidney disease (N=37153)	≥ 90	NS		NS		NS	

Reference	Population	Reference GFR (ml/min/ 1.73m^2)	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
[464]	Adults with type 1 + type 2 diabetes (N=3288)	≥ 90	1.28 (1.02, 1.60)		2.58 (2.05, 3.25)		6.42 (4.25, 9.71)	
Outcome: risk of cardiovascular mortality								
[268]	Heart failure (N=2680)	> 90	NS	NS	1.54 (1.22, 1.94), p<0.001	1.86 (1.47, 2.36, p<0.001)		
[677]	Acute MI and LVEF ≤ 40% (N=2183)	≥ 75	-	NS	NS	1.96 (1.39, 2.76)		
Outcome: risk of cardiovascular events								
[561]	Hypertension + high risk for CVD (N=31897, ALL-HAT)	≥ 90	1.08 (1.01, 1.15), p=0.027		1.35 (1.24, 1.46), p<0.001			
[677]	Acute MI and LVEF ≤ 40% (N=2183)	≥ 75	-	Recurrent MI: NS heart failure: NS	Recurrent MI: 1.42 (1.03, 1.96) heart failure: NS	Recurrent MI: NS Heart failure: NS		
[640]	Type 2 Diabetic (N=4421)	≥ 90	NS		NS		3.23 (1.74,5.99)	-
[229]	Kaiser Permanente cohort (N= 1120295)	≥ 60	-	-	1.4 (1.4-1.5)	2.0 (1.9-2.1)	2.8 (2.6-2.9)	3.4 (3.1-3.8)
[438]	Adults with DM, HYP, or family history of DM, HYP, or kidney disease	≥ 90	NS		1.37 (1.13, 1.67), p=0.001		NS	

Reference	Population	Reference GFR (ml/min/ 1.73m^2)	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
	(N=37153)							
Outcome: risk of hospitalisation								
[229]	Kaiser Permanente cohort (N= 1120295)	≥ 60	-	-	1.1 (1.1-1.1)	1.5 (1.5-1.5)	2.1 (2.0-2.2)	3.1 (3.1-3.3)
Outcome: risk of ESRD								
Reference	Population	Reference GFR (ml/min/1.73m^2)	GFR 89-75 (95% CI)	GFR 74.9-60 (95% CI)	GFR 59-45 (95% CI)	GFR 45-30 (95% CI)	GFR 29-15 (95% CI)	GFR < 15 (95% CI)
[561]	Hypertension + high risk for CVD (N=31897, ALL-HAT)	≥ 90	2.90 (1.90, 4.67), p<0.001		20.33 (12.74, 32.42), p<0.001			
[640]	Type 2 diabetes (N=4421)	≥ 90	NS		3.34 (2.06, 5.42)		27.3 (15.6, 47.8)	-
Outcome: risk of peripheral arterial disease								
Reference	Population	Reference GFR (ml/min/ 1.73m^2)	GFR 89-75 (95% CI)	GFR 74.9-60 (95% CI)	GFR 59-45 (95% CI)	GFR 45-30 (95% CI)	GFR 29-15 (95% CI)	GFR < 15 (95% CI)
[714]	ARIC cohort (N=14280)	≥ 90	NS		1.58 (1.14, 2.17)			-

Shaded boxes indicate GFR spanning different GFR ranges.
ALL-HAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARIC = Atherosclerosis Risk in Communities; LVEF = left ventricular ejection; MI = myocardial infarction.

P.5.1.5 Section 5.1.5: From evidence to recommendations

There has been debate about the implications of having a reduced GFR and, in particular, whether a stable GFR that does not change over time is associated with adverse health outcomes.

Not all studies stratified patients according to whether or not they had diabetes and this may affect estimates of the risk of death.

The evidence suggested that if the GFR is less than 60 ml/min/1.73m^2, then there is an increased risk of mortality which is seen in all age groups.

There was limited evidence about outcomes in older people. However, given that they are at increased absolute risk of mortality and cardiovascular events it was agreed that even small increases in relative risk in older people are of significance.

The GDG considered that the evidence suggested that the risk of mortality and cardiovascular events increased considerably when the GFR was less than 45 ml/min/1.73m^2. This led to the proposal to adopt the sub-division of stage 3 CKD into stages 3A and 3B, defined by an eGFR 45–59 ml/min/1.73m^2 and 30–44 ml/min/1.73m^2 respectively.

The GDG noted that although it has been suggested that the rate of progression of CKD in black and ethnic minority groups may be higher than in Caucasians, as yet there is no published evidence to support this.

It was noted that the presence of proteinuria was associated with a doubling of CVD risk and mortality at all levels of GFR. This led to the proposal to adopt the suffix '(p)' notation to denote the presence of proteinuria when staging CKD. Evidence from longitudinal population studies and from meta-analysis of progression risk and level of proteinuria suggested that an ACR ≥30 mg/mmol should be used as a marker of the increased risk (roughly equivalent to a PCR ≥50 mg/mmol or proteinuria values ≥0.5 g/day).

The GDG agreed not to recommend age-related decision points for eGFR. However, it seemed clear that in people aged >70 years, an eGFR in the range 45–59 ml/min/1.73m^2, if stable over time and without any other evidence of kidney damage is unlikely to be associated with CKD-related complications.

P.5.1.6 Section 5.1.6: RECOMMENDATIONS

R20 Use the suffix '(p)' to denote the presence of proteinuria when staging CKD.

R21 For the purposes of this classification define proteinuria as urinary albumin:creatinine ratio (ACR) ≥30 mg/mmol or PCR ≥50 mg/mmol (approximately equivalent to urinary protein excretion ≥0.5 g/24 hours).

R22 Stage 3 CKD should be split into two subcategories defined by:

- GFR 45–59 ml/min/1.73m^2 (stage 3A) and
- GFR 30–44 ml/min/1.73m^2 (stage 3B).

R23 At any given stage of CKD, management should not be influenced solely by age.[h]

Stages of chronic kidney disease (updated)		
Stage[(a)]	**GFR (ml/min/1.73m^2)**	**Description**
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decrease in GFR, with or without other evidence of kidney

[h] In people aged >70 years, an eGFR in the range 45-59 ml/min/1.73m^2, if stable over time and without any other evidence of kidney damage, is unlikely to be associated with CKD-related complications.

3B	30-44	damage
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

(a) Use the suffix (p) to denote the presence of proteinuria when staging CKD (recommendation R20)

P.5.2 Section 5.2: Who should be tested for CKD?

P.5.2.1 Section 5.2.7: RECOMMENDATIONS

R24 Monitor glomerular filtration rate (GFR) in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors and lithium. Check GFR at least annually in people receiving long-term systemic non-steroidal anti-inflammatory drug (NSAID) treatment.

R25 Offer people testing for CKD if they have any of the following risk factors:

- diabetes
- hypertension
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
- structural renal tract disease, renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus (SLE)
- family history of stage 5 CKD or hereditary kidney disease
- opportunistic detection of haematuria or proteinuria.

R26 In the absence of the above risk factors, do not use age, gender, or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD.

P.6 Section 6: Defining progression of CKD and the risk factors associated with progression

P.6.1 Section 6.1: Defining progression

P.6.1.1 Section 6.1.1: Clinical introduction

The Renal NSF adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD.[482] Whilst the beauty of this classification is its simplicity, this is also its weakness. The clinical features and course of CKD are dependent on a number of factors including the underlying cause, severity and associated conditions of the underlying cause.

Although the classification of CKD into 5 stages has been widely adopted, it has been criticised as not being sufficiently sophisticated for clinical needs. The existing classification is neither staged according to age, nor according to level of proteinuria. All patients, regardless of age, gender and

proteinuria/albuminuria are considered to have at least moderately severe CKD when their GFR is <60 ml/min/1.73m^2. This guideline recommends that stage 3 should be subdivided into 3A and 3B, and that the suffix '(p)' in parenthesis be adopted in the different stages to underline the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes (Table 209).

Table 209: Modifications to existing stages of chronic kidney disease

Stage	Description	GFR (ml/min/1.73m^2)	Proteinuria
1	Kidney damage with normal or increased GFR	≥90	Use '(P)' to denote when significant proteinuria is present ACR ≥30 mg/mmol)
2	Kidney damage with mild reduction in GFR	60–89	
3A	Moderate reduction in GFR	45–59	
3B		30–44	
4	Severe reduction in GFR	15–29	
5	Kidney failure	<15 (or dialysis)	

CKD is defined as either kidney damage (proteinuria, haematuria or anatomical abnormality) or GFR <60 ml/min/1.73m^2 present on at least 2 occasions for ≥90 days.

A further criticism of the existing classification of CKD has been the suggestion that loss of GFR is a feature of ageing and that many people classified as stage 3 CKD are merely exhibiting a normal ageing process. The effects of normal ageing on renal function are controversial. Data from some studies suggest that the decline in GFR with increasing age may be largely attributable to comorbidities such as hypertension and heart failure. Loss of renal function may not, therefore, be an inevitable consequence of ageing.[203,389,391] This was supported by studies demonstrating no or very little decline in GFR in the older population with longitudinal follow-up.[260]

P.6.1.2 Section 6.1.6: RECOMMENDATIONS

R27 Take the following steps to identify progressive CKD:

- Obtain a minimum of three glomerular filtration rate(GFR) estimations over a period of not less than 90 days.
- In people with a new finding of reduced eGFR, repeat the estimated glomerular filtration rate (eGFR) within 2 weeks to exclude causes of acute deterioration of GFR, eg acute kidney injury or initiation of ACEI/ARB therapy.
- Define progression as a decline in eGFR of >5 ml/min/1.73m^2 within one year, or >10 ml/min/1.73m^2 within 5 years.
- Focus particularly on those in whom a decline of GFR continuing at the observed rate would lead to the need for renal replacement therapy within their lifetime by extrapolating the current decline.

P.6.2 Section 6.2: Risk factors associated with progression of CKD

P.6.2.1 Section 6.2.5: From evidence to recommendations

Despite the lack of evidence for urinary outflow tract obstruction for progression of CKD, the GDG consensus was that obstruction to outflow would lead to progression of CKD. Therefore it was agreed that urinary outflow tract obstruction should be considered as a risk factor.

P.6.2.2 Section6.2.6: RECOMMENDATIONS

R28 Work with people who have risk factors for progression of CKD to optimise their health. These risk factors are:

- cardiovascular disease
- proteinuria
- hypertension
- diabetes
- smoking
- black or Asian ethnicity
- chronic use of non-steroidal anti-inflammatory drugs (NSAIDs)
- urinary outflow tract obstruction.

R29 In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible fall in glomerular filtration rate (GFR). Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression.

P.7 Section 7: Referral criteria

P.7.1 Section 7.1: Indications for referral to specialist care

P.7.1.1 Section 7.1.6: RECOMMENDATIONS

R30 People with CKD in the following groups should normally be referred for specialist assessment:

- stage 4 and 5 CKD (with or without diabetes)
- heavy proteinuria (ACR ≥70 mg/mmol, approximately equivalent to PCR ≥ 100 mg/mmol, or urinary protein excretion ≥1g/24 hours) unless known to be due to diabetes and already appropriately treated
- proteinuria (ACR ≥30 mg/mmol, approximately equivalent to PCR ≥ 50 mg/mmol, or urinary protein excretion ≥0.5 g/24 hours) together with haematuria
- rapidly declining eGFR (>5 ml/min/1.73m^2 in one year, or >10 ml/min/1.73m^2 within 5 years)
- hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also NICE clinical guideline 34, 'Hypertension: management of hypertension in adults in primary care')
- people with, or suspected of having rare or genetic causes of CKD
- suspected renal artery stenosis.

R31 Consider discussing management issues with a specialist by letter or telephone in some cases where it may not be necessary for the person with CKD to be seen by the specialist.

R32 Once a referral has been made and a plan jointly agreed, it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified.

R33 Take into account the individual's wishes and comorbidities when considering referral.

R34 People with CKD and renal outflow obstruction should be referred to urological services, unless urgent medical intervention is required, e.g. for treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload.

P.8 Section 8: Self management

P.8.1 Section 8.1: Modification of lifestyle

P.8.1.1 Section 8.1.1: Clinical introduction

The increased prevalence of CKD has been linked to lifestyle-related factors such as hypertension and diabetic nephropathy (see NICE Clinical Guideline 34 'Management of hypertension in adults in primary care'; NICE Clinical Guideline 66 'Management of Type 2 diabetes'; NICE Clinical Guideline 15 'Diagnosis and management of Type 1 diabetes in children, young people and adults'; and NICE Clinical Guideline 43 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children'). [472,473,475,476] Smoking has been associated with more severe proteinuria and progression of renal failure. In rat models of CKD, exercise training has been shown to be renoprotective. [349] The association between obesity, smoking, physical activity and CKD therefore may be important. Equally there may be insufficient adjustment of potential confounders. Obesity leads to CKD through diabetes and hypertension but is it an independent risk factor for CKD? Similarly although it is suggested that smoking and physical inactivity contribute to progression of CKD, is this a direct or indirect effect, and is there a relationship to gender? [242]

P.8.1.2 Section 8.1.6: RECOMMENDATIONS

R35 Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking.

P.8.2 Section 8.2: Dietary intervention and renal outcomes

P.8.2.1 Section 8.2.1: Clinical Introduction

A real concern with respect to dietary protein restriction in people with CKD is the spontaneous reduction in dietary protein intake with declining GFR. Spontaneous dietary protein intakes were observed to fall from 1.1 g/kg/day for patients with creatinine clearances >50 ml/min to 0.85 g/kg/day at 25–50 ml/min, 0.70 g/kg/day at 10–25 ml/min and 0.54 g/kg/day at <10 ml/min.[291]

The use of protein restricted diets for people with CKD has remained a controversial issue.[378] In the 1960s people were often following the Giovanetti Diet, containing 20g high biological value protein to cover the essential amino acid requirements, but as dialysis became available its use has declined.[227] In the 1980s there was a renewed interest in low protein, high energy diets as partially nephrectomised rats showed that protein restriction delayed the progression of renal disease. This led in 1985 to the National Institute of Health (NIH) in the USA commissioning a large multi-centre

study – the Modification of Diet in Renal Disease (MDRD) study[378] – to investigate the effect of protein restriction on the progression of kidney disease. Although the results of this trial did not support severely protein restricted diets, the findings focussed on improvement in blood pressure control and the prevention of complications due to uraemia and malnutrition and dietary phosphorus restriction to prevent renal bone disease.[343]

P.8.2.2 Section 8.2.2: Methodology

The Pedrini et al. systematic review compared a low protein diet (LPD) with a usual diet (5 RCTs, N=1413, protein intake in the LPD group ranged from 0.4 to 0.6 g/kg/day, follow-up range 18–36 months) in people with nondiabetic moderate CKD (all participants analysed had a GFR <55 ml/min).[535]

The Foque et al. systematic review was an update on the Pedrini et al. analysis and it compared LPD with a usual diet (8 RCTs, N=1524, protein intake in the LPD group ranged from 0.3–0.6 g/kg/day, follow-up range 12–24 months) in people with nondiabetic CKD (5/8 studies were conducted in people with stage 4–5 CKD).[207]

The Roberston et al. systematic review compared LPD (0.3–0.8 g/kg/day protein intake) with a usual diet (protein intake 1–2 g/kg/day) in people with type 1 diabetic nephropathy (8 studies, N=322) or type 2 diabetic nephropathy (1 study, N=263). The mean follow-up ranged from 4.5 months to 4 years.[576]

Most of the trial pooled in these meta-analyses were conducted in people with stage 4–5 CKD. The effect of LPD compared with a usual protein diet on renal disease progression in adults with diabetic or nondiabetic nephropathy is summarised in Table 210 at the end of the evidence statements.

P.8.2.3 Section 8.2.4: Evidence statements

Renoprotective effects of low protein diets (LPDs) compared with usual protein diets (UPDs) in nondiabetic nephropathy

Protein intake was significantly lower in the LPD group compared with UPD, but compliance was a problem as few achieved the target protein level in the LPD group.[207,535]

Low protein diets: risk of ESRD or death

There was a significant reduction in the occurrence of death or ESRD in people with nondiabetic renal disease on a LPD compared with those on a UPD.[207,535] Sensitivity analysis showed that stricter LPD (0.3 to 0.6 g/kg/day) significantly reduced the risk of death or ESRD compared with a UPD, whereas there was NS difference in risk when the protein restriction was moderate (0.6 g/kg/day).[207] (Level 1+)

Low protein diets: changes in GFR, creatinine clearance, or serum creatinine

There was no meta-analysis for this outcome. A beneficial effect on GFR change with a LPD was seen in 1 RCT[290] and a possible beneficial effect was seen in the MDRD study.[343] One RCT showed NS differences in creatinine clearance between LPD and UPD.[722] One RCT showed NS differences between LPD and UPD for serum creatinine increases,[396] whereas another RCT[587] showed a beneficial effect of a LPD on serum creatinine changes. (Level 1+)

Low protein diets: change in mid-arm circumference

This outcome was not assessed in either systematic review. Extraction of data from one included trial showed that there were NS differences between UPD group (N=32) and LPD group (N=33) for changes in mid-arm circumference.[722] (Level 1+)

Renoprotective effects of low protein diets compared with usual protein diets in diabetic nephropathy

The intended protein intake in the LPD group ranged from 0.3–0.8 g/kg/day, however compliance was low as the actual protein intake ranged from 0.6–1.1 g/kg/day.[576]

Low protein diets: risk of ESRD or death

The risk of ESRD or death (adjusted for baseline cardiovascular disease) was significantly lower in people with type 1 diabetes and nephropathy randomised to LPD compared with UPD (1 study, N=82).[576] (Level 1+)

Change in GFR

In people with type 1 diabetes and nephropathy, there was NS improvement in GFR in those randomised to a LPD compared with UPD (7 RCTs, N=222). There was significant heterogeneity (I2=62%, p=0.01). In people with type 2 diabetes and nephropathy, there was a NS improvement in GFR in the LPD group compared with the UPD (1 RCT, N=160). Another RCT in people with type 2 diabetes and nephropathy (N=37) showed a similar decline in GFR in the LPD compared with the UPD group. In one RCT in which type 1 and type 2 diabetic people with nephropathy were combined (N=80), there were NS differences in GFR decline between those randomised to LPD compared with a UPD.[576] (Level 1+)

Quality of life

No study assessed this outcome.

Nutritional status

Nine studies assessed nutritional status, but only 1 study found evidence of malnutrition as serum pre-albumin and albumin significantly decreased in the LPD group compared with the UPD group.[576] Four studies showed NS differences between LPD or UPD groups for serum albumin.[175,246,447,558] (Level 1+)

Changes in mid-arm circumference

This outcome was not assessed in the Robertson et al. meta-analysis. Extraction of data from a trial included in the meta-analysis showed that there were NS differences between LPD group (N=41) and UPD (N=41) for changes in mid arm circumference in people with type 1 diabetes and nephropathy.[246] (Level 1+)

Table 210: Effect of a low protein diet (LPD) compared with a usual protein diet (UPD) on renal disease progression in adults with diabetic or nondiabetic nephropathy (95% confidence intervals)

Reference	Population	Outcome	LPD vs. UPD
[535]	Nondiabetic CKD: 5 RCTs, N=1413	ESRD or death	RR 0.67 (0.50-0.89), p=0.007 in favour of LPD
[207]	Nondiabetic CKD: 8 RCTs, N=1524	ESRD or death	RR 0.69 (0.56-0.86), p=0.0007 in favour of LPD
[207]	Nondiabetic CKD: 3 RCTs, N=1116	ESRD or death	RR 0.76 (0.54-1.05), p=0.1 NS LPD (0.6 g/kg/day) vs. UPD
[207]	Nondiabetic CKD: 5 RCTs, N=408	ESRD or death	RR 0.65 (0.49-0.86), p=0.002 LPD (0.3-0.6 g/kg/day) vs. UPD
[535]	Nondiabetic CKD: 2 RCTs, N=649	GFR change	Beneficial/possibly beneficial effect
[535]	Nondiabetic CKD: 1 RCT, N=65	Changes in creatinine clearance	NS
[535]	Nondiabetic CKD: 2 RCTs, N=704	Changes in serum creatinine	1 RCT=NS 1 RCT=benefit
[576]	Type 1 diabetic nephropathy: 1 RCT, N=82	ESRD or death	RR 0.23 (0.07-0.72), p=0.01 (adjusted for baseline CVD) in favour of LPD
[576]	Type 1 diabetic nephropathy: 7 RCTs, N=222	GFR change	WMD +0.14 ml/min/month (-0.06 to +0.34) NS Heterogeneity (p=0.01)
[576]	Type 2 diabetic nephropathy: 2 RCTs, N=197	GFR change	LPD: -0.4 ml/min/month UPD: -0.3 ml/min/month (NS, 1 RCT, N=160) LPD: -0.51 ml/min/month UPD: -0.52 ml/min/month (NS, 1 RCT, N=37)
[576]	Type 1 + type 2 diabetic nephropathy: 1 RCT, N=80)	GFR change	LPD: -0.48 ml/min/month UPD: -0.50 ml/min/month NS

WMD = weighted mean difference

P.8.2.4 Section 8.2.5: From evidence to recommendations

It was noted that the dietary protein intake often declines as people get older and that this is likely to occur in people with CKD.

It was noted that apart from the risks of malnutrition, low protein diets are usually unpalatable and are time consuming to adhere to as all portions must be weighed. These aspects are likely to affect the quality of life of people with CKD and therefore any recommendations about dietary restriction must have a sound evidence base.

The GDG also noted that adequate iron in the diet is important in CKD and restricting protein intake may adversely influence iron intake.

The GDG agreed that the studies combined in the meta-analysis by Pedrini et al. were too heterogeneous in terms of the severity of the underlying CKD for the analysis and conclusions to be appropriate. It was also noted that some of the studies were carried out at a time when the pharmacological management, particularly the use of ACE inhibitors, was likely to be different. The individual studies were examined and the GDG agreed that there was limited evidence that there may be a benefit of protein restriction in patients with stage 4 and 5 CKD, but the evidence did not point to an optimal protein intake.

P.8.2.5 Section 8.2.6: RECOMMENDATIONS

R36 Where the clinician in discussion with the patient has decided that dietary intervention to influence progression of CKD is indicated, an appropriately trained professional should discuss the risks and benefits of dietary protein restriction, with particular reference to retarding the progression of disease versus protein-calorie malnutrition.

R37 Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented.

R38 Offer dietary advice to people with progressive CKD concerning potassium, phosphate, protein, calorie and salt intake when indicated.

P.9 Section 9: Blood pressure control

P.9.1 Section 9.1: Blood pressure control in people with CKD

P.9.1.1 Section 9.1.1: Clinical introduction

General aspects of blood pressure management will not be covered in this guideline but for advice relating to measuring blood pressure and lifestyle interventions to reduce blood pressure please see NICE clinical guideline 34 ('Hypertension: management of hypertension in adults in primary care'). Although the hypertension guideline did not recommend home monitoring recent data shows that self-measurement leads to less medication use than clinic blood pressure measurement without leading to significant differences in outpatient values of blood pressure.[700]

P.9.1.2 Section 9.1.5: From evidence to recommendations

Evidence relating to lifestyle advice (such as salt restriction) in blood pressure control can be found in the NICE clinical guideline 34 on hypertension.[475]

P.9.1.3 Section 9.1.6: RECOMMENDATIONS

R39 In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.

R40 In people with diabetes and CKD or when the ACR is ≥70 mg/mmol, (approximately equivalent to urinary protein excretion ≥1.0 g/24 h) aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg.

P.9.2 Section 9.2: Choice of anti-hypertensive agents for blood pressure control in people with CKD

P.9.2.1 Section 9.2.1: Clinical introduction

In general, different classes of anti-hypertensives reduce blood pressure to a similar degree, and a number of trials of anti-hypertensive therapy have shown that reduction of blood pressure reduces the risk of end stage kidney disease and of cardiovascular disease regardless of the class of agent employed.[541,585,633,708,721] NICE recommends that for people newly diagnosed with hypertension, those younger than 55 years should be started on an ACE inhibitor or ARB, and those either over 55 years or of black ethnicity should be started on either a calcium-channel blocker or thiazide-type diuretic.[475] Where blood pressure remains uncontrolled additional classes of anti-hypertensives such as alpha-blockers and beta-blockers are recommended. Hypertension is extremely common in people with CKD and the mean number of antihypertensive agents prescribed is associated with the stage of CKD, increasing as GFR falls.[653]

Existing guidelines are quite clear that certain anti-hypertensive agents have specific benefits in patients with additional comorbidities and it is well known that ACEI/ARBs have additional benefits over and above blood pressure control in people with diabetes. The UK CKD guidelines[589] recommend that ACEI/ARBs should be used as first line therapy only for people with diabetic kidney disease and for those with proteinuria (urine PCR >100 mg/mmol) and this was endorsed by the UK consensus conference. Although the evidence is less clear in non-diabetic kidney disease with lesser degrees of proteinuria the Quality and Outcomes Framework requires the use of ACEI/ARBs in people with stage 3–5 CKD hypertension and proteinuria. The CARI guidelines[105] recommend that regimens including ACEI/ARBs are more effective in slowing progression of non-diabetic CKD, and that combination of ACEIs and ARBs slow progression more effectively than either single agent. They also conclude that ACEI/ARBs are more effective than beta-blockers and dihydropyridine calcium channel blockers, and that beta-blockers may be more effective than dihydropyridine calcium channel blockers.

What are the most appropriate antihypertensive drugs to reduce the risk of progression of CKD and to decrease mortality in adults with CKD?

P.9.2.2 Section 9.2.2: Methodology

Six systematic reviews[107,307,316,335,359,657] and ten RCTs[2,19,149,370,420,540,561,593,594,725] compared the use of ACE inhibitors and/or ARBs with placebo or other antihypertensive agents (alpha or beta blockers, calcium channel blockers, thiazide diuretics). Most trials used non-ACEI or non-ARB antihypertensive agents in both arms to achieve blood pressure control and to ascertain if ACEI or ARBs provided renoprotective effects beyond blood pressure control.

The sample sizes in these studies ranged from N=180 to 39485 and the duration of the trials ranged from 6 months to 6 years. The mean age of study participants was under sixty years of age, with the exception of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

(ALLHAT) study,[561] in which the mean age was 67 or 70 in each treatment arm. The studies were also quite heterogeneous in terms of the population studied – diabetic nephropathy or nondiabetic CKD.

Two studies[540,593] were rejected as important features such as the number of people in each trial arm, intention to treat analysis, baseline characteristics, or statistical power estimations were not provided. The study by Marin et al.[420] was excluded as it was not blinded and was underpowered for the mortality outcome. A systematic review of ten RCTs[316] comparing combination therapy ACEI + ARB versus monotherapy (ACEI or ARB) in adults with diabetic nephropathy was rejected because the quality of each included trial was not assessed; the primary outcome (proteinuria change) had significant heterogeneity and there was no heterogeneity analysis for sub-group analyses. Studies included in meta-analysis were only 8–12 weeks long. There was wide variation in the dosage of ACEI and ARB, and few studies titrated to the maximum tolerated dose.

P.9.2.3 Section 9.2.3: Health economics methodology

Seven papers[219,262,274,580,592,611,695] were included that evaluated ACEI (Table 211) and a further 10 papers[99,142,265,516,516,517,579,645,661,703] evaluated ARBs (Table 212), all based on randomised controlled trials. Two more studies[141,647] evaluated ACEI or ARB treatment based on meta-analysis of RCTs.

Most papers evaluated the drugs in the context of diabetic nephropathy.

Of the papers appraised, only 3 were UK-based. Studies which are not UK-based may not be easily transferable to a UK setting. However, the UK studies reached similar conclusions to the North American and European studies.

Table 211: Summary of economic evaluations of ACEI to treat CKD

Study and country	ACEI	Authors	Time horizon (years)	Discount rate (% p.a.)	
				Costs	Effects
DNCSG (diabetes)	Captopril				
UK		[262]	4	6	6
Italy		[219]	10	5	5
US		[580]	Lifetime	5	5
REIN (non-diabetes)	Ramipril				
US		[592]	Lifetime	5	5
Germany		[611]	3	5	5
AIPRI (various)	Benazepril				
Netherlands		[695]	10	5	5
US		[274]	7	5	5

Table 212: Summary of economic evaluations of ARB to treat CKD

Study and country	ARB	Authors	Time horizon (years)	Discount rate (% p.a.)	
				Costs	Effects
IDNT (diabetes)	Irbesartan				

Study and country	ARB	Authors	Time horizon	Discount rate (% p.a.)	
UK		[516]	10	6	1.5
US		[579]	3, 10 & 25	3	3
Switzerland		[517]	25	5	5
Canadian		[142]	25	3	3
Belgium and France		[516]	Lifetime	3	3
RENAAL (diabetes)	Losartan				
UK		[703]	Lifetime	3.5	3.5
US		[265]	3.5	3.5	NM
Switzerland		[661]	3.5	NM	NM
Canadian		[99]	4	NM	NM
France		[645]	5	NM	NM

NM= not modelled

P.9.2.4 Section 9.2.4: Evidence statements

Renoprotective effects of ACE inhibitors or ARBs compared with placebo/no treatment

One systematic review [657] investigated the renoprotective effects of ACE inhibitors or ARBs compared to placebo or no treatment in adults with diabetic kidney disease.

Another systematic review (49 RCT, N=6181, trial durations 1–12 months) assessed changes in proteinuria in people with renal disease of various causes randomised to ARBs versus placebo, calcium channel blockers, or ACE inhibitors. It also assessed combination therapy (ACEI + ARB) versus ACEI or ARB monotherapy.[359] In the combination therapy comparisons, few trials titrated the ACEI and ARB dosage to the maximum tolerated doses.

The Ramipril Efficacy in Nephropathy (REIN) RCT compared an ACE inhibitor (ramipril) with placebo in non-diabetic adults with CKD (N=352) stratified by baseline proteinuria: stratum one covered 1–2.9 g/24 h[594] and stratum two ≥3 g/24 h.[2] Both trial arms received non-ACEI antihypertensive agents to control blood pressure.

Risk of ESRD

There was a significant reduction in the risk of ESRD with ACEI (10 studies, N=6819, RR 0.60, 95% CI 0.39–0.93) or ARB (3 studies, N=3251, RR 0.78, 95% CI 0.67–0.91) compared with placebo or no treatment.[657] (Level 1++)

In adults with non-diabetic CKD and baseline proteinuria 1–2.9 g/24 h, ramipril (ACE inhibitor) significantly reduced the risk of progression to ESRD by 56% compared to placebo.[594] For adults with baseline proteinuria ≥3 g/24 h, ramipril significantly reduced the risk of ESRD or doubling of serum creatinine (18/78 ramipril versus 40/88 placebo, p=0.04). A higher baseline urinary protein excretion rate was associated with a higher risk of reaching the combined endpoint in the placebo group, but not in the ramipril group.[2] (Level 1+)

Doubling of serum creatinine

There was NS reduction of the risk of doubling of serum creatinine for ACEI compared to placebo or no treatment.[657] (Level 1++)

There was a significant reduction in the risk of the doubling of serum creatinine with ARB compared with placebo/no treatment (3 studies, N=3251, RR 0.79, 95% CI 0.67–0.93).[657] (Level 1++)

Progression from micro- to macroalbuminuria

ACEI (17 studies, N=2036, RR 0.45, 95% CI 0.29–0.69) or ARB (3 studies, N=761, RR 0.49, 95% CI 0.32–0.75) significantly reduced the risk of progression from micro- to macroalbuminuria compared with placebo. There was NS reduction in progression from micro- to macroalbuminuria for ACEI vs. ARB (1 study, N=41).[657] (Level 1++)

In the REIN study, ramipril significantly reduced the risk of progression to overt proteinuria by 52% compared to placebo.[594] (Level 1+)

Regression to normoalbuminuria

ACEI (16 studies, N=1910, RR 3.06, 95% CI 1.76–5.35) or ARB (2 studies, N=670, RR 1.42, 95% CI 1.05–1.93) significantly increased regression from micro- to normoalbuminuria compared with placebo or no treatment. There was NS difference in regression to normoalbuminuria for ACEI compared with ARB.[657] (Level 1++)

Changes in proteinuria

In adults with baseline proteinuria 1–2.9 g/24 h, median proteinuria increased from baseline by 15% in the placebo group and decreased by 13% in the ramipril group (p=0.003).[594] In adults with baseline urinary protein excretion rate ≥3 g/24 h, urinary protein excretion decreased from baseline by 35% and 55% at month 3 and month 36, respectively (p=0.002), while urinary protein excretion did not change in the placebo arm.[2] (Level 1+)

ARBs significantly decreased proteinuria compared with placebo (6 RCTs, N=2994, 5–12 month follow-up, ratio of means 0.66 (96% CI 0.63–0.69) or CCBs.[359] (Level 1+)

Change in GFR

In adults with baseline urinary protein excretion 1–2.9 g/24 h, there was NS difference in the mean GFR decline per month in the ramipril versus the placebo group.[594] In those with baseline urinary protein excretion ≥3 g/24 h, the mean GFR decline was significantly slower in the ramipril group than the placebo group (0.53 vs. 0.88 ml/min per month, p=0.03).[2] (Level 1+)

Renoprotective effects of ACE inhibitors or ARBs compared to other antihypertensive agents

One meta-analysis[107] compared ACE inhibitors or ARBs against other antihypertensive drugs in adults with CKD. Trials of ACE inhibitors were not separated from trials of ARBs, thus confounding factors such as differences in drug tolerability could not be separated. Even with these caveats, this meta-

analysis was interesting as it provided sensitivity analyses in diabetic and non-diabetic populations. (Level 1+)

One RCT conducted in hypertensive diabetic adults with CKD compared an ACE inhibitor with a calcium channel blocker.[149] One RCT conducted in hypertensive nondiabetic populations with CKD compared an ACE inhibitor with a beta blocker.[725] One RCT compared an ACE inhibitor with a thiazide diuretic conducted in a mixed diabetic/nondiabetic population with CKD.[561] (Level 1+)

Risk of ESRD

In the meta-analysis, ACEI or ARB use was associated with a significant reduction in the occurrence of ESRD compared with other antihypertensive drugs (13 trials (N=37,089, RR 0.87, 95% CI 0.75–0.99, p=0.04). When trials in diabetic and nondiabetic populations were separated from each other, there was NS difference between ACEI or ARB compared with other antihypertensive drugs [107]. (Level 1+)

In a nondiabetic population, there was no significant difference between ramipril and metoprolol in risk reduction for ESRD alone.[725] (Level 1+)

Doubling of serum creatinine

There was NS reduction in the risk of doubling serum creatinine with ACEI or ARBs compared with other antihypertensive drugs (11 trials, N=3376).[107] (Level 1+)

Progression from micro- to macroalbuminuria

In a hypertensive diabetic population with microalbuminuria, there was NS difference in progression to macroalbuminuria between people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).[149] (Level 1+)

Regression to normoalbuminuria

There was NS difference in regression to normoalbuminuria between people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).[149] (Level 1+)

Changes in proteinuria

ACEI or ARBs showed a small reduction in urine albumin excretion compared with other antihypertensive treatments (44 trials, N=5266, mean difference –15.73, 95% CI –24.72 to –6.74, p=0.001). However, there was significant interstudy heterogeneity (p<0.0001) and small study bias (p=0.001).[107] In participants with diabetic CKD, a small reduction in urine albumin excretion was noted for ACEI or ARBs compared with other antihypertensive treatments (34 trials, N=4772, mean difference –12.68, 95% CI –21.68 to –2.74). In studies only including people without diabetes, ACEI or ARBs were associated with a significant reduction in albumin excretion compared with other antihypertensive agents (8 trials, N=414 mean difference –32.30, 95% CI –49.18 to –15.42).[107] (Level 1+)

In a hypertensive diabetic population with microalbuminuria (N=180), there was NS difference between albumin excretion rates in people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).[149] (Level 1+)

ARBs significantly decreased proteinuria compared with calcium channel blockers (5 RCTs, N=1432, 5–12 month follow-up, ratio of means 0.62 (95% CI 0.55–0.70).[359] (Level 1+)

ACEI + ARB combination therapy significantly decreased proteinuria compared with ARB monotherapy (7 RCTs, N=362, ratio of means 0.75, 95% CI 0.61–0.92).[359] (Level 1+)

There was NS effect on proteinuria of ACEI versus ARB.[359] (Level 1+)

Change in GFR

ACEI or ARBs had NS effect on GFR decline compared with other antihypertensive treatments.[107] (Level 1+)

By contrast, in a black nondiabetic hypertensive population, the mean GFR decline was significantly slower in the ramipril group (ACEI) than the metoprolol group (beta blocker) (1.81 vs. 2.42 ml/min /1.73m^2, p=0.007).[725] (Level 1+)

Cardiovascular protection by ACE inhibitors or ARBs compared to placebo or no treatment: all-cause mortality

There was NS decrease in the risk of all-cause mortality with ACEI or ARB or combination ACEI + ARB compared with placebo/no treatment. In a subgroup analysis of studies which used ACEI at the maximum tolerable dose compared with placebo/no treatment, there was a significant decrease in the risk of all-cause mortality (5 studies, N=2034, RR 0.78, 95% CI 0.61–0.98).[657] (Level 1++)

In the REIN study, there was NS difference between ramipril and placebo for all-cause mortality. However, the study was underpowered for this outcome.[2] (Level 1+)

Nonfatal MI and fatal coronary heart disease

There was no significant difference between ramipril and placebo for non-fatal cardiovascular events.[2] (Level 1+)

Cardiovascular protection by ACE inhibitors or ARBs compared to other antihypertensive agents: all-cause mortality

There was NS difference between ramipril (ACEI) and metoprolol (beta blocker) for all-cause mortality.[725] (Level 1+)

Nonfatal MI and fatal coronary heart disease

There was NS difference in the risk for MI or CHD between lisinopril (ACEI) or chlorthalidone (thiazide diuretic) for people with mild or moderate/severe renal impairment.[561] (Level 1+)

There was NS difference between ramipril (ACEI) and metoprolol (beta blocker) for cardiovascular events or cardiovascular mortality.[725] (Level 1+)

Combined CVD: composite of nonfatal MI, fatal CHD, coronary revascularisation, hospitalised angina, stroke, fatal/hospitalised/treated non-hospitalised heart failure, peripheral arterial disease

People with mild (OR 1.09, 95% CI 1.02–1.17, p=0.015, N=13,259) or moderate/severe renal impairment (OR 1.12, 95% CI 1.01–1.25, p=0.038, N=4146) receiving lisinopril (ACEI) had a significantly increased chance of combined CVD than those receiving chlorthalidone (thiazide diuretic).[561] (Level 1+)

Stroke

There was NS difference in the risk for stroke between lisinopril or chlorthalidone for those with mild or moderate/severe renal impairment.[561] (Level 1+)

Heart failure

People with moderate/severe renal impairment receiving lisinopril had significantly increased odds of heart failure compared with those receiving chlorthalidone (OR 1.29, 95% CI 1.06–1.58, p=0.011).[561] (Level 1+)

Adverse events with ACE inhibitors or ARBs compared to placebo or no treatment: cough

ACEI use was associated with a significant increase in the risk of cough compared to placebo (10 studies, N=7087, RR 3.17, 95% CI 2.29–4.38). ARB or combination ACEI + ARB use were NS associated with cough compared with placebo.[657] (Level 1++)

Hyperkalaemia

There was NS difference in the risk of hyperkalaemia for ACEI versus placebo/no treatment. There was a significant increase in the risk of hyperkalaemia with ARB compared with placebo (2 studies, N=2287, RR 5.41, 95% CI 1.87–15.65).[657] (Level 1+)

Adverse events from ACE inhibitors or ARBs compared to other antihypertensive agents: cough

The proportion of patients reporting cough was significantly higher in those receiving ramipril (ACEI) than metoprolol (beta blocker) (54.9% vs. 41.5 %, p<0.05).[725] (Level 1+)

Hyperkalaemia

There was no hyperkalaemia in people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).[149] (Level 1+)

There was no significant difference in hyperkalaemia incidence between ramipril and metoprolol.[725] (Level 1+)

Reno-protective effects of ACEI or ARBs in non-diabetic patients with urinary protein excretion of <1 g/day

There were two meta-analyses that used a database of patient-level data from 9 published and 2 unpublished RCTs comparing an ACEI with either placebo or active controls in non-diabetics.[307,335] In

this database 40% of the included patients had proteinuria of <500 mg/day and 60% had proteinuria of ≥500 mg/day.[335]

Three papers on one RCT (AASK trial) compared an ACEI with either a beta-blocker or a calcium channel blocker, in a population of African-American non-diabetic adults with CKD.[19,370,725] One third of the patients included in this trial had a baseline PCR >0.22 (a value corresponding approximately to the threshold of 300 mg/day for clinically significant proteinuria) and the remaining two thirds had a PCR of ≤0.22.[19]

Risk of ESRD

The unadjusted relative risk of developing ESRD was lower in the ACEI group, becoming significantly less than 1 at a baseline urinary protein excretion of >1.0 g/day. For people with baseline urinary protein excretion of <0.5 g/day the relative risk of ESRD was 1.01 (95% CI 0.44–2.32), and 0.66 (95% CI 0.28–1.56) for patients with baseline urinary protein excretion of 0.5–1.0 g/day.[307] (Level 1+)

There was significant interaction between baseline urine protein and ACEI therapy (interaction p=0.003). The Kent et al. meta-analysis did not find any additional benefit of ACEI therapy among patients with proteinuria <500 mg/day, even amongst those at high risk for progression to ESRD. In people with urinary protein ≥500 mg/day, a substantial treatment effect was seen across all risk groups.[335] (Level 1+)

From the results of the AASK trial, the reduction in risk for developing the clinical outcomes of ESRD or a halving of GFR was 38% (95% CI 13–56%) for the ACEI vs. the calcium-channel blocker comparison group and among participants with a PCR >0.22, the reduction in risk of developing the clinical outcomes was 48% (95% CI 20–66%, p=0.003).[19] Another analysis of this trial data found that the baseline level of urinary protein excretion was an independent predictor of change in GFR and the risk of developing ESRD.[370] The risk of developing ESRD was found to be similar in all treatment groups: ACEI, calcium channel blocker and beta-blocker, although the magnitude of the change in GFR at 6 months was greater in the calcium channel blocker treatment group than the ACEI or beta-blocker treatment groups. (Level 1+)

Protein excretion rate

One RCT[19] found a significantly greater reduction in proteinuria in the ACEI treated group compared with the control calcium channel blocker group both above and below a baseline PCR of 0.22. Among those with PCR <0.22, the rate at which participants developed PCR ≥0.22 was 56% (95% CI 37–69%) lower for the ACEI group than for the calcium-channel blocker group.[19] (Level 1+)

One of the meta-analyses found a significantly greater mean decrease in proteinuria in the ACEI group than in the control group of 0.46 g/day (95% CI 0.33–0.59 g/day).[307] (Level 1+)

Change in GFR

The analyses of the AASK trial all found the baseline proteinuria level to be a strong predictor of GFR decline, with higher baseline proteinuria levels associated with significantly greater declines in GFR.[19,370,725] The Agodoa et al. study reported a significantly greater GFR decline over three years in the ACEI treated group compared with the calcium channel blocker group in patients who had a

baseline PCR of ≤0.22. By contrast, the GFR decline was significantly slower in the ACEI group than the calcium channel blocker group in people who had a baseline PCR >0.22 (corresponding to a urinary protein excretion of >300 mg/day, p=0.006). (Level 1+)

A second paper found that baseline proteinuria did not influence the comparison of ACEI to beta-blocker with respect to GFR change.[725] (Level 1+)

P.9.2.5 Section 9.2.5: Health economics evidence statements

ACE inhibitors

Economic evaluations based on the DNCSG study have looked at the costs and effects in several healthcare settings:

- In the US, Rodby et al.[580] estimated an absolute direct cost saving of $32,550 and indirect savings of $84,390 per patient with type 1 diabetes over a lifetime; year of costing not stated. For type 2 diabetes, the direct cost savings totalled $9900 per patient and $45,730 for indirect costs. For type 1 diabetes patients, the estimated increase in life years was 0.2 over a 5 year period and 2.15 over a 31 year period with the use of captopril therapy compared with the placebo. The savings in dialysis years were 0.18 over 5 years and 0.72 over 31 years. For type 2 diabetes patients, the estimated average increase in life years over 12 years was 1.04, and 0.29 dialysis years.
- In Italy, Garattini et al.[219] used a 10-year horizon, calculated direct costs savings of L8,450,965 per patient (total direct cost savings of 28%, 1993 values). Captopril was also more effective than placebo by resulting 20.01 discounted dialysis-years avoided (DYA) per 100 patients.
- In the UK, Hendry et al.[262] estimated that discounted cost savings associated with ACE inhibitor treatment over 4 years for a cohort of 1000 patients would total £0.95 million (year of costing not stated). Life years saved over 4 years for a cohort of 1000 patients treated with an ACE inhibitor was estimated to be 195.

Economic evaluations based on the REIN study:

- In the US, Ruggenenti et al.[592] estimated the difference in overall per year costs between ramipril and the control group was –$2422 in the GFR model and –$4203 in the events model. Both models constructed by the authors also predicted a reduced and delayed progression to ESRD and a prolonged patient survival in the ramipril group.
- In Germany, Schadlich et al.[611] estimated incremental cost-effectiveness ratios (ICERs) for ramipril of approximately –DM76,700 for 1 year, –DM80,660 for 2 years and –DM81,900 for 3 years.

Economic evaluations based on the AIPRI study:

- In the Netherlands, van Hout et al.[695] projected an overall savings of US$4200 per patient over the 3-year period and when a 10-year time span was applied, similar results were shown with approximately US$28,000 cost saving per patient comparing benazepril and placebo. It was also estimated that 51.2% of placebo patients and 63.3% pf patients treated with benazepril would never require dialysis at any point.
- In the US, Hogan et al.[274] over 7 years of analysis, showed that patients randomised to antihypertensive treatment with concomitant benazepril therapy incurred on average incurred

lower medical costs than patients prescribed antihypertensive treatment without benazepril by US$12,991 (1999 values) and obtained an additional 0.091 QALYs.

ARBs

Economic evaluations based on the IDNT study have looked at the costs and effects in several healthcare settings:

- Data for ESRD projections have been published for Belgium and France but not for the UK, USA or Canada. As the transition probabilities from the states progressing to ESRD were taken from the IDNT rather than country-specific data, the model produced the same projections for all countries. Over a 10-year time span the mean time to onset of ESRD was 8.23 years for irbesartan, 6.82 years for amlodipine and 6.88 years for the control. The mean cumulative incidence of ESRD over the 10-year time span was 45% for control, 49% for amlodipine and 36% for irbesartan. Although the UK and the USA (and Canada) were simulated using the same model and transition probabilities, it could be expected that the results might be the same for these countries.
- In summary, life expectancy was improved in the irbesartan group compared to amlodipine and control groups in all the papers reviewed. However, in the UK study by Palmer et al.[516] life expectancy projections were reported only in relative terms, comparing irbesartan to amlodipine and control. Treatment with irbesartan was projected to extend life further than that with either amlodipine or control.
- For cost analysis, irbesartan resulted in cost savings very early, usually within 2–3 years of treatment for all settings. In the UK, cost savings due to avoided or delayed ESRD were evident after 3 years compared to the amlodipine group and after 4 years compared to the control group.
- Based on the published evidences from various studies, it appears that irbesartan has a valuable role in reducing the huge clinical and economic burden associated with ESRD in patients with type 2 diabetes, hypertension and overt nephropathy.

Economic evaluations based on the RENAAL study have looked at the costs and effects in several healthcare settings. Treatment with losartan was associated with a reduced number of ESRD days by an average of 46.9 days per patient compared to the placebo and a net saving of:

- C$6,554 in Canada[99]
- US$7,058 in the USA[265]
- €5,835 in France,[645]
- CHF6511 in Switzerland.[661]

Also, the UK study projected £6622 net savings and the mean number of life years saved were 0.44 years.[703]

An economic evaluation based on the IDNT and IRMA-2 study has looked at the costs and effects in the Canadian healthcare setting.[141] Treatment with irbesartan (early and late initiation of treatment) was compared to conventional care of people with hypertension and type 2 diabetes. The early irbesartan strategy was dominant over both the late irbesartan and conventional antihypertensive therapy strategies. Initiating irbesartan therapy during advanced overt nephropathy was dominant over conventional antihypertensive therapy. Late irbesartan treatment resulted in a mean of 0.16 life years gained and $14,300 cost savings compared with conventional antihypertensive therapy. When

irbesartan treatment is initiated early, there is a mean of 0.45 life-years gained per patient and a cost saving of $54,100 compared with starting irbesartan treatment later. The early irbesartan strategy was found to be cost-saving by year 5 compared with conventional treatment strategy and year 6 compared with the late irbesartan treatment strategy.

These economic evaluations using different time horizons suggest ARBs versus conventional therapy is cost saving for type 2 diabetes nephropathy patients, mainly because of the high costs of dialysis and transplantation.

An economic evaluation based on a meta-analysis of randomised studies investigated the effects of ACEI/ARB therapy on the incidence of ESRD in patients with diabetic nephropathy in both a Greek and a US healthcare setting[647]. ACEI or ARB therapy was compared with alternative treatment regimens that did not include these drugs. For patients receiving ACEI or ARBs, the net cost saving was more than $2000 per patient in both settings, but these results were not statistically significant and there was heterogeneity between trials. The study demonstrates that treating patients with diabetic nephropathy with agents that block the renin-angiotensin system as part of the treatment regimen is cost effective, resulting in a 23% reduction in the incidence of ESRD and in net cost savings for the insurance system organisations.

Conclusion

All of the economic evaluations found that these drugs confer both health gains and net cost savings compared with conventional (non-ACE inhibitor) therapy, ie they are dominant therapies.

P.9.2.6 Section 9.2.6: From evidence to recommendations

When considering the evidence, the GDG noted that many of the studies combine people with types 1 and 2 diabetes and very few of the studies include older people. The GDG also noted that certain studies such as AASK were in defined populations and extrapolation of findings into the UK population should be viewed with caution.

When considering the evidence about the effects of ACEI/ARBs, the GDG noted that the beneficial effects appeared to be more closely related to the presence or absence of proteinuria rather than blood pressure control.

In order to confidently detect changes in the rate of decline of GFR the GDG agreed that studies must be of duration ≥3 years.

The GDG agreed that the evidence of benefit of ACEI/ARBs in people with diabetes and micro- or macroalbuminuria was strong.

RCTs and meta-analyses of RCTs that have analysed cardiovascular outcomes in patients with CKD/proteinuria treated with renin-angiotensin blockade have shown significant reduction in cardiovascular outcomes in both diabetic nephropathy and nondiabetic nephropathy. Benefits in terms of reduction in proteinuria and reduction in progression of CKD have also been shown. RAS blockade confers benefit in reducing adverse cardiovascular events in patients with proteinuria when compared with control therapy; a similar benefit is seen in reducing the risk for heart failure in diabetic nephropathy and total cardiovascular outcomes in nondiabetic nephropathy patients. These

results might suggest that renin-angiotensin system blockade may be more beneficial in CKD patients with proteinuria.

On the basis of the evidence, the GDG agreed that the threshold level of proteinuria at which ACEI/ARBs should be recommended in non-diabetic people without hypertension was an ACR ≥70 mg/mmol (approximately equivalent to urinary protein excretion of ≥1 g/day). The threshold level of proteinuria at which ACEI/ARBs should be recommended in non-diabetic people with hypertension was an ACR of ≥30 mg/mmol (approximately equivalent to urinary protein excretion of ≥0.5 g/day).

It is possible that ACEI/ARB therapy in people with CKD without diabetes and with lower levels of proteinuria may also be beneficial but there is no evidence in this group at present. The GDG agreed that clinical trials examining the effects in these people were needed as a matter of urgency

The GDG agreed that there was no evidence to suggest an advantage of one particular ACE inhibitor over and above another or of ARB over and above an ACE inhibitor. There was also no evidence to suggest increased effectiveness of combining an ACE inhibitor with an ARB over and above the maximum recommended dose of each individual drug. However, the health economic evidence suggested increased cost-effectiveness for ACEIs versus ARBs, indicating an ACE inhibitor should first be prescribed, switching across to an ARB if the ACEI is not tolerated due to non-renal side affects.

P.9.2.7 Section 9.2.7: RECOMMENDATIONS

R41 When implementing blockade of the renin-angiotensin system, start treatment with an ACE inhibitor first then move to an ARB if the ACE inhibitor is not tolerated.

R42 Offer ACE inhibitors/ARBs to people with diabetes and ACR >2.5 mg/mmol (men) or >3.5 mg/mmol (women) irrespective of the presence of hypertension or CKD stage.

R43 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and hypertension and ACR ≥ 30 mg/mmol (approximately equivalent to PCR 50 mg/mmol or more, or urinary protein excretion of 0.5 g/24 h or more).

R44 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and ACR 70 mg/mmol or more (approximately equivalent to PCR 100 mg/mmol or more, or urinary protein excretion of 1 g/24 h or more) irrespective of the presence of hypertension or cardiovascular disease.

R45 Offer non-diabetic people with CKD and hypertension and ACR less than 30 mg/mmol (approximately equivalent to PCR less than 50 mg/mmol, or urinary protein excretion less than 0.5 g/24 h) a choice of antihypertensive treatment according to NICE clinical guidance on hypertension (NICE clinical guideline 34) to prevent or ameliorate progression of CKD.

R46 When using ACE inhibitors/ARBs, titrate them to the maximum tolerated therapeutic dose before adding a second-line agent.[i]

R47 To improve concordance, inform people who are prescribed ACE inhibitors or ARB therapy about the importance of:

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[i] There is insufficient evidence to recommend the routine use of spironolactone in addition to ACE inhibitor and ARB therapy to prevent or ameliorate progression of CKD.

- achieving the optimal tolerated dose of ACE inhibitor/ARB, and
- monitoring eGFR and serum potassium in achieving this safely.

P.9.3 Section 9.3: Practicalities of treatment with ACEI/ARBs in people with CKD

P.9.3.1 Section 9.3.6: RECOMMENDATIONS

R48 In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACEI/ARB therapy and repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase.

R49 ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically >5.0 mmol/l).

R50 When hyperkalaemia precludes use of ACEI/ARBs, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration re-checked .

R51 Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of ACEI/ARBs but more frequent monitoring of serum potassium concentration may be required.

R52 Stop ACEI/ARB therapy if the serum potassium concentration rises to above 6.0 mmol/l and other drugs known to promote hyperkalaemia have been discontinued.

R53 Following the introduction or dose increase of ACEI/ARB, no modification of the dose is required if either the GFR decrease from pre-treatment baseline is <25% or the plasma creatinine increase from baseline is <30%.

R54 If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not modify the ACE/ARB dose if the change in eGFR <25% or change in plasma creatinine is <30%.

R55 If the eGFR change is ≥25% or change in plasma creatinine is ≥30%:

- investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDS)
- if no other cause for the deterioration in renal function is found, stop the ACEI/ARB therapy or halve the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required.

P.9.4 Section 9.4: Considerations of age in prescription of ACEI/ARB therapy

P.9.4.1 Section 9.4.1: Clinical introduction

Although there is much clinical evidence to support the use of ACE inhibitors and ARBs to delay progression of renal disease in people with chronic kidney disease, few studies include older people with CKD in the study population. The older population are also more prone to reduced volume status and sodium depletion, have greater comorbidity and are more likely to be taking concurrent

medications making them potentially more susceptible to the adverse effects of ACEI/ARBs. Indeed, there is a perception that ACEI or ARB treatment puts the older person at greater risk for adverse events such as acute kidney failure/injury, hypotension, falls, and reduced quality of life. Few studies have described the progression of CKD in older community based individuals, and none have confirmed the widely held belief that low GFR is associated with a rapid progression of kidney dysfunction in older people.[85,260] Should we reconsider the role of renin-angiotensin system blockade to prevent progression of CKD in the context of the older population in which the burden of overt proteinuric nephropathies is believed to be lower than in other populations?

Is there a greater potential risk of further deterioration of renal function because of the high prevalence of renal stenotic atherosclerotic lesions and very frequent concomitant use of diuretics and nonsteroidal anti-inflammatory drugs?

P.9.4.2 Section 9.4.2: Methodology

An open-label RCT conducted in Japanese adults with nondiabetic, hypertensive renal disease (N=141, age range 60–75 years, mean age 67, mean follow-up 3.1 years) compared the effect of an ARB (candesartan) with conventional antihypertensive treatment on cardiovascular events in those with and without a previous history of cardiovascular disease.[469] This small, open-label RCT was terminated after 3 years, due to the increasing prevalence of ARBs as physicians were switching from conventional treatment to ARBs.

One post-hoc analysis of the RENAAL trial (N=1513, mean follow-up 3.4 years) examined the effect of increasing age on the efficacy and safety of losartan versus placebo (conventional antihypertensive treatment).[723] The trial participants had type 2 diabetes with nephropathy and were stratified by age: ≤57 years (N = 505), age >57 to 65 years (N= 587), and age >65 years (N= 421). Although this study lacked the statistical power necessary to assess efficacy of losartan treatment in each of the three increasing age ranges, it did analyse the interaction between age and losartan treatment for the outcomes of death, hyperkalaemia, and adverse events such as acute renal failure. The oldest participant in the study was 74 years old, and thus this study lacks data on very elderly people.

A retrospective cohort analysis of people >65 years of age was conducted to investigate whether receiving an ACE inhibitor at hospital discharge following an acute myocardial infarction increased one year survival rates in people with poor renal function (serum creatinine >3 g/dl, N=1582) compared with people with better renal function (serum creatinine ≤3 mg/dl, N=19,320).[210] This study was limited by lacking data on protein excretion rate and the use of serum creatinine alone as an indicator of renal function.

P.9.4.3 Section 9.4.3: Health economics methodology

No health economics papers were found to review.

P.9.4.4 Section 9.4.4: Evidence statements

All-cause mortality

The treatment effect of losartan on risk of death in a population with diabetic nephropathy did not significantly differ by age (p=0.695 adjusted for treatment group, region, proteinuria, albumin,

creatinine, haemoglobin). In all three age groups (people ≤57 years, age >57 to 65 years, or >65 years) there was NS difference in risk of death between losartan and placebo.[723] (Level 2+)

In a nondiabetic Japanese population with renal disease (N=141), no deaths occurred in the people without a past history of cardiovascular disease (treated with candesartan or conventional therapy).

- Four deaths occurred in the group with a past history of CVD treated with candesartan.
- Four deaths occurred in the group with a past history of CVD treated with conventional therapy (p value not stated).[469]72 (Level 1+)

Stroke

In people with nondiabetic, hypertensive renal disease, with or without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of stroke.[469] (Level 1+)

Myocardial infarction (MI)

In people with nondiabetic, hypertensive renal disease, with or without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of MI.[469] (Level 1+)

Congestive heart failure

In people with nondiabetic, hypertensive renal disease and a previous history of CVD, candesartan treatment (4/33) significantly decreased the incidence of congestive heart failure compared with conventional treatment (13/38, p<0.05). In people without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of congestive heart failure.[469] (Level 1+)

One-year survival following acute MI

The receipt of an ACE inhibitor at hospital discharge was associated with a 37% increase in 1-year survival for patients with poor renal function (serum creatinine >3 mg/dl, N=1582, mean age 72. HR 0.63, 95% CI 0.48–0.84, p value not stated). The receipt of an ACE inhibitor at hospital discharge was associated with a 16% increase in 1-year survival for patients with better renal function (serum creatinine ≤ 3 mg/dl, N=19,320, mean age 75, HR 0.84, 95% CI 0.77-0.92, p value not stated).[210] (Level 2+)

Adverse events (acute renal failure or ESRD)

Older patients were no more susceptible to experiencing adverse events from losartan than younger people. In all three age groups (people ≤57 years, age 57–65 years, or >65 years) there was NS difference in incidence of adverse events between losartan or placebo.[723] (Level 2+)

Hyperkalaemia

Losartan was associated with a greater rate of hyperkalaemia. This effect was present in all age ranges. Thus, increasing age did not significantly increase the risk of hyperkalaemia from losartan.[723] (Level 2+)

P.9.4.5 Section 9.4.5: From evidence to recommendations

It was noted that in the observational studies those with better renal function were more likely to receive ACEI/ARBs (60% versus only 30% in those with poor renal function) and this has the potential to bias the interpretation of these studies.

None of the people in the studies were over 75 years of age. Thus there is a lack of evidence for changes in the risk/benefit of ACEI/ARB therapy in people over this age; however, the GDG felt that in the absence of evidence of harm people above this age should not be denied the benefits of ACEI/ARB therapy.

P.9.4.6 Section 9.4.6: RECOMMENDATIONS

R56 Where indicated, the use of ACEI/ARBs should not be influenced by a person's age as there is no evidence that their appropriate use in older people is associated with a greater risk of adverse effects.

P.9.5 Section 9.5: The role of aldosterone antagonism in people with CKD

P.9.5.1 Section 9.5.1: Clinical introduction

Aldosterone is thought to contribute to progressive renal disease. Studies in experimental rat models showed that aldosterone may contribute to the progression of kidney disease and antagonists of aldosterone may reduce proteinuria and retard the progression of kidney disease independently of effects on blood pressure.[577,578] Plasma aldosterone level was shown to correlate with the rate of progression of kidney disease and the increase in rate of kidney disease progression caused by high protein intake was attributable in part to aldosterone.[263,586,707] Although ACEI/ARBs inhibit the renin-angiotensin system, they do not efficiently decrease plasma aldosterone. Haemodynamic and humoral actions of aldosterone have important clinical implications for the pathogenesis of progressive renal disease and consequently may influence future antihypertensive strategies. Although ACEI/ARBs are effective in preventing disease progression there may be additional benefit from concurrent aldosterone-receptor blockade.[183] To date there has been limited research into the use of spironolactone, an aldosterone receptor antagonist, to reduce aldosterone escape during treatment with ACEI/ARBs in adults with CKD.

In adults with proteinuric or non-proteinuric CKD, does treatment with (a) spironolactone alone, (b) combinations of spironolactone and ACE inhibitors, (c) combinations of spironolactone and ARBs, or (d) combinations of spironolactone and ACE inhibitors and ARBs decrease mortality and reduce the risk of progression of CKD compared with placebo or other antihypertensive agents?

P.9.5.2 Section 9.5.2: Methodological introduction

There were no studies in a CKD population that compared spironolactone with alpha- or beta-blockers, calcium channel blockers, or diuretics. There were no studies that investigated spironolactone in adults with non-proteinuric CKD.

Three double-blind RCTs examined the effects of spironolactone in addition to treatment with ACE inhibitors and/or ARBs in adults with diabetic nephropathy[588,692] and in a mixed population of diabetic and nondiabetic nephropathy.[124] One open label randomised study compared the addition of spironolactone to conventional ACEI and ARB therapy with conventional therapy alone in nondiabetic adults with proteinuric CKD.[74] One study that compared spironolactone with cilazapril (ACEI) in a diabetic population with proteinuric nephropathy was rejected because it lacked intention-to-treat analysis, and concealment and blinding were not stated.[560]

The results of these studies should be viewed with caution as the sample sizes were small (N= 21–165) and duration of these trials (2 months–1 year) was short. None of the studies reported cardiovascular outcomes, mortality, or progression to ESRD.

P.9.5.3 Section 9.5.3: Health economics methodology

No health economics papers were found to review.

P.9.5.4 Section 9.5.4: Evidence statements

Renoprotective effects of spironolactone: reduction in proteinuria or albuminuria

In two RCTs conducted in diabetic adults with nephropathy concomitantly treated with ACE inhibitors or ARBs, spironolactone significantly reduced albuminuria compared with placebo.[588,692] (Level 1+)

In a nondiabetic CKD population, addition of spironolactone to ACEI or ARB therapy resulted in a significant reduction in proteinuria. The reduction in proteinuria was significantly greater in people with GFR <60 ml/min/1.73m^2 than in people with GFR >60 ml/min /1.73m^2. By contrast, proteinuria did not change from baseline in people treated with ACEI or ARB therapy alone.[74] (Level 1+)

In an RCT conducted in a diabetic/nondiabetic mixed CKD population, the reduction in 24-hour urinary protein excretion was significantly greater in either the ramipril + spironolactone group or in the ramipril + irbesartan + spironolactone group, compared to the ramipril group. Compared with the ramipril + irbesartan group, there was a greater reduction in 24-hour urinary protein excretion in the ramipril + irbesartan + spironolactone group. There was NS difference in proteinuria reduction between ramipril + spironolactone group and ramipril + irbesartan + spironolactone groups. The spironolactone-induced decrease in proteinuria was similar regardless of presence of diabetes.[124] (Level 1+)

Change in GFR

In three studies,[74,124,588] there was no significant difference in GFR decline in patients receiving spironolactone with ACEI or ARB therapy compared to the control (placebo or no treatment). (Level 1+)

By contrast, van den Meiracker et al. reported that spironolactone significantly decreased the eGFR compared to placebo. (Level 1+)

Toxicity of spironolactone: hyperkalaemia

Treatment with spironolactone in addition to ACEI and ARB therapy seemed to be associated with a higher incidence of hyperkalaemia, although these studies were probably too underpowered to detect a significant difference between treatment groups.

Four people receiving spironolactone + conventional therapy and two people receiving conventional therapy alone developed hyperkalaemia (no p value stated).[74] (Level 1+)

Three patients receiving spironolactone developed hyperkalaemia.[124] (Level 1+)

One patient treated with spironolactone was excluded from the study due to hyperkalaemia.[588] (Level 1+)

Despite decreasing the dose of spironolactone from 50–25 mg/d, five patients treated with spironolactone were excluded from the study due to hyperkalaemia compared to only one patient in the placebo group (no p value stated).[692] (Level 1+)

P.9.5.5 Section 9.5.5: From evidence to recommendation

The GDG noted that all the evidence on this topic comes from short duration trials that are small and under powered. Very few of the trials reported on relevant outcomes such as cardiovascular events and none reported on progression of CKD.

Because of the limitations of trial design and their duration, the GDG agreed that a recommendation about the use of spironolactone should not be made based on the evidence regarding effects on proteinuria. Reference is made in a footnote to the recommendations on ACE inhibitors/ARBs.

The GDG noted that hyperkalaemia was more common in people treated with spironolactone.

P.10 Section 10: Reducing cardiovascular disease

P.10.1 Section 10.1: Statin therapy and reduction in proteinuria

P.10.2 Section 10.2: Lipid lowering in people with CKD

P.10.2.1 Section 10.2.1: Clinical introduction

The benefits of lipid-lowering therapy in people with pre-existing cardiovascular disease are clear and very well described.[1,117,256] Although people with CKD are at increased risk of CVD and might

reasonably be expected to also benefit from the effects of lipid lowering therapy, the published randomised controlled trials have largely excluded people with most types of kidney disease. Furthermore the expected positive association between blood cholesterol levels and cardiovascular outcomes were not observed in studies conducted in people receiving haemodialysis.[712] Studies in animal models suggest that treatment of dyslipidaemia should have beneficial effects on progression of CKD.[330,331,497] A systematic review pooling the literature from all human studies that were conducted before 2000 (n=404 participants) suggested that similar benefits might accrue in humans. The studies included evaluated multiple classes of medications, including statins, fibric acid derivatives, and probucol.[213]

The spectrum of dyslipidaemia in CKD is distinct from the general population and varies with stage of CKD and presence of diabetes and/or nephrotic syndrome. Plasma triglycerides start to increase early in CKD and show the highest concentrations in nephrotic syndrome and people receiving dialysis. HDL-cholesterol concentrations are generally reduced compared with people without CKD and the distribution of subfractions is different, leading to impairment in reverse cholesterol transport and promoting atherosclerosis. Although elevated plasma LDL-cholesterol is a feature of nephritic syndrome, it is not typical of advanced CKD but, like HDL-cholesterol, there are qualitative changes in the LDL subfractions with an increase in those that are highly atherogenic. Lipoprotein (a), a risk factor for CVD in the general population is also influenced by CKD. Levels rise early in CKD and are mostly influenced by the degree of proteinuria. The hallmarks of uraemic dyslipidaemia are hypertriglyceridaemia, increased remant lipoproteins, reduced HDL-cholesterol, increased atherogenic sub-types of LDL-cholesterol, increased lipoprotein (a) and increased apolipoprotein A-IV.[363]

The optimal targets for plasma lipids in people with CKD are not yet known. Statins are effective at lowering total and low-density lipoprotein (LDL)-cholesterol and fibrates reduce plasma triglyceride concentrations and raise HDL-cholesterol. Nicotinic acid appears most suited to the dyslipidaemia of CKD because it raises HDL-cholesterol, lowers lipoprotein (a), reduces triglycerides and shifts the LDL-cholesterol fraction to less atherogenic particles. SIGN guidelines recommend treatment with statins for people with stage 1–3 CKD and a predicted 10 year cardiovascular risk of ≥20%, irrespective of baseline lipid parameters. The CARI guidelines suggest that statins may retard progression of renal failure but make no specific recommendation. The UK CKD guidelines recommend that people with CKD and coronary disease should be treated according to existing guidelines and those who do not have evidence of coronary disease should be treated according to their estimated risk, using the Joint British Societies Guidelines (recognising that these guidelines specifically exclude CKD from their remit).

In adults with CKD and dyslipidaemia, do lipid lowering agents (statins, fibrates, fish oils) decrease cardiovascular disease risk and all-cause mortality compared with placebo or each other?

P.10.2.2 Section 10.2.2: Methodology

Hydroxymethyl glutaryl CoA reductase inhibitors (statins), fibric acid derivates (fibrates), and omega-3 fatty acids (fish oils) are antilipemic therapies that may reduce the risk of cardiovascular disease by decreasing triglyceride or LDL cholesterol levels and increasing HDL cholesterol levels. There were very few trials of antilipemic therapies in non-dialysis CKD populations. There were no head-to-head

studies of the three antilipemic therapies in adults with CKD. There were no studies that examined the efficacy of omega-3 fatty acids to reduce the risk of cardiovascular disease in adults with CKD.

A post-hoc analysis of the Veterans' Affairs High-Density Lipoprotein Intervention RCT (VA-HIT: N=1046, follow-up 5.3 years),[678] compared a fibrate (gemfibrozil) to placebo for cardiovascular outcomes in men with a history of coronary heart disease and creatinine clearance <75 ml/min. This study is limited by a lack of baseline proteinuria data, all the participants were men and the population did not include people with severe renal disease. Creatinine clearance overestimates GFR and it is likely that the participants identified as having chronic renal insufficiency could have had lower renal function than estimated. Also, the creatinine concentrations were not standardised between centres or calibrated against a reference standard.

A systematic review assessed cardiovascular outcomes, changes in GFR and 24-hour proteinuria in people with CKD randomised to statins or placebo/no treatment (50 studies, N=30,144, follow-up ranged from 2–60 months).[656] Subgroup analysis was performed in people with pre-dialysis CKD (26 studies), people undergoing dialysis (11 studies) and renal transplant recipients (17 studies).

A post-hoc analysis of the Scandinavian Simvastatin Survival RCT (4S: N=2314, follow-up 5.5 years, mean age 60 years) compared cardiovascular outcomes in people with coronary heart disease, raised cholesterol, and GFR <60 ml/min/1.73m^2 randomised to placebo or simvastatin. This study lacked proteinuria data and cause of CKD. Estimated, rather than measured, GFR was used to assess renal function.[119]

P.10.2.3 Section 10.2.3: Health economics methodology

There were no health economics papers found to review.

P.10.2.4 Section 10.2.4: Evidence statements

Fibrates versus placebo: Primary endpoint: nonfatal MI or death from coronary disease (including fatal MI, sudden death, death during a coronary intervention, death from other coronary causes)

In men with CrCl ≤75 ml/min (N=1046), gemfibrozil significantly reduced the risk of nonfatal MI or death from coronary disease compared to treatment with placebo (adjusted HR 0.74, 95% CI 0.56–0.96, p=0.02, NNT = 16).[678] (Level 1+)

Secondary endpoints: major cardiovascular events (fatal coronary disease, nonfatal MI, or stroke)

In men with CrCl ≤75 ml/min (N=1046), gemfibrozil significantly reduced the risk of major cardiovascular events compared with placebo (adjusted HR 0.75, 95% CI 0.59–0.96, p=0.02).[678] (Level 1+)

There was NS difference between placebo and gemfibrozil[678] for risk of:

- non-fatal myocardial infarction
- all-cause mortality
- stroke
- adverse events: myositis. (Level 1+)

Adverse events: creatinine > 0.5 mg/dl higher from baseline

The incidence of sustained elevations in serum creatinine (>0.5 mg/dl higher from baseline) was significantly higher among gemfibrozil recipients compared with placebo (5.9% vs. 2.8%, p=0.02).[678] (Level 1+)

Adverse events: rhabdomyolysis

There were no cases of rhabdomyolysis in either the placebo or gemfibrozil group.[678] (Level 1+)

Statins versus placebo

Refer to Table 213 for a summary of the efficacy of statins versus placebo in people with CKD.

Compared with placebo, statins significantly reduced the risk of:

- all-cause mortality[119,656] (Level 1+)
- cardiovascular mortality[656] (Level 1++)
- non-fatal cardiovascular events[656] (Level 1++)
- major coronary events (coronary mortality, non-fatal acute MI, resuscitated cardiac arrest, definite silent MI).[119] (Level 1+)

There were NS differences between statins and placebo for stroke.[119] (Level 1+)

Adverse events

Rates of discontinuation of study drug therapy because of adverse events were similar in simvastatin and placebo groups.[119] (Level 1+)

Table 213: Effect of statins versus placebo on cardiovascular outcomes in adults with CKD.

Study	Population	Outcome	N total participants	Effect size	Heterogeneity (% I2)
[656]	Pre-dialysis CKD (Stage 1-4)	All-cause mortality	18,781	RR 0.81 (95% CI 0.74 to 0.89), p <0.001, mostly driven by Pravastatin Pooling Project	0 NS
[119]	GFR <75 ml/min/1.73m^2 with coronary heart disease, raised low-density lipoprotein cholesterol (LDL-C)	All-cause mortality	2314	HR 0.69 (95% CI 0.54-0.89)	Not applicable
[119]	GFR <60 ml/min/1.73m^2 with coronary heart disease, raised LDL-C	All-cause mortality	508	HR 1.232 (1.024-1.117) [sic] NS [sic]	Not applicable

Study	Population	Outcome	N total participants	Effect size	Heterogeneity (% I2)
[656]	Pre-dialysis CKD (stage 1-4)	Cardiovascular mortality	18,085	RR 0.80 (95% CI 0.70 to 0.90), p <0.001, mostly driven by Pravastatin Pooling Project	0 NS
[656]	Pre-dialysis CKD (stage 1-4)	Non-fatal cardiovascular events	19,363	HR 0.851 (0.921-1.128) [sic] NS	30.7 NS
[119]	GFR <60 ml/min/1.73m^2 with coronary heart disease, raised LDL-C	Major coronary events	508	HR 0.65 (95% CI 0.46-0.92)	Not applicable
[119]	GFR <75 ml/min/1.73m^2 with coronary heart disease, raised LDL-C	Major coronary events	2314	HR 0.67 (95% CI 0.56-0.79)	Not applicable

P.10.2.5 Section 10.2.5: From evidence to recommendations

The main reason for examining the evidence in this area was the anecdotal observation that in people on dialysis, statins do not appear to offer the benefits seen in other groups. This may be due to the fact that there is reduced long-term survival in this particular group of people and that this may mask any beneficial effect of statins.

The GDG discussed whether CKD itself should be considered a risk factor for cardiovascular disease and should influence the use of statins as primary preventative therapy. In the absence of evidence that CKD is a causal risk factor for cardiovascular disease it was decided that the GDG should recommend that the use of statins for primary prevention of cardiovascular disease should be determined using existing risk tables bearing in mind the fact that a different table should be used for people with diabetes[480]. It was further recommended that studies are needed to assess the effect of CKD on cardiovascular risk.

On the basis of the evidence of effect in secondary prevention of cardiovascular disease the GDG recommended that lipid lowering therapy should be prescribed in people who have experienced a cardiovascular event. The evidence showed that there was benefit from statins in all people not just those with elevated lipid concentrations.

The lack of statistically significant differences observed in subgroup analyses may be due to the small numbers of people in these groups and the consequent lack of statistical power.

The GDG noted that there is a large international multicentre trial in progress which addresses the effects of lipid lowering with simvastatin and ezetimibe on outcomes in people with CKD without established coronary heart disease.

The GDG concluded that there was no evidence that statins had detrimental effects on kidney function in people with CKD, but it was noted that there appeared to be an increase in creatinine concentrations in people prescribed fibrates.

P.10.2.6 Section 10.2.6: RECOMMENDATIONS

R57 The use of statin therapy for the primary prevention[j] of CVD in people with CKD should not differ from its use in people without CKD and should be based on existing risk tables for people with and without diabetes. It should be understood that the Framingham risk tables significantly underestimate risk in people with CKD.[k]

R60 Offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values

P.10.3 Section 10.3: Antiplatelet therapy and anticoagulation in people with CKD

P.10.3.1 Section 10.3.1: Clinical introduction

People with CKD paradoxically have both thrombotic and bleeding tendencies. Bleeding symptoms are usually mild, correlate best with prolonged bleeding times, and tend to become more prevalent with increasing severity of CKD.[234,559,648] Factors involved include anaemia, platelet defects, abnormal function of von Willebrand factor, uraemic toxins and endothelial factors, such as increased production of nitric oxide.[189,233,450,567] The greater risk of thrombotic events has been attributed to higher levels of procoagulant activity in people with CKD. Described abnormalities include increased levels of thrombin concurrent with high levels of fibrinogen, and elevated levels of factors VII and VIII.

CKD is an independent risk factor for the development of generalised atherosclerosis and coronary artery disease, and is associated with a worse prognosis following cardiovascular events. People with CKD have a higher risk of morbidity and death related to cardiovascular disease than of progression to end stage renal failure. Large clinical trials in the general population have demonstrated that antiplatelet agents reduce the risk of cardiovascular events, and may improve patency rates following revascularisation therapy. What evidence is there that the benefits of antiplatelet therapy in people with CKD outweigh the potential risks of bleeding complications?

P.10.3.2 Section 10.3.2: Methodology

There were very few studies conducted in populations with non-ESRD CKD that assessed the safety and efficacy of antiplatelet agents (aspirin, clopidogrel, dipyramidole, glycoprotein IIb/IIIa inhibitors). There were no studies that investigated anticoagulants (warfarin) to prevent mortality and cardiovascular events in people with CKD.

[j] There is insufficient evidence to support the routine use of statins to prevent or ameliorate progression of CKD.

[k] The use of statins for the primary prevention of CVD in people with CKD should be informed by the Study of Heart and Renal Protection (SHARP) reported in: Baigent C, Landry M. Study of heart and renal protection. Kidney International (2003); 63: S207–S210.

One post hoc analysis of the double blind Clopidogrel in Unstable Angina to Prevent Recurent Events RCT (CURE, N=12,253, mean follow-up 9 months) compared clopidogrel with placebo in patients with various levels of renal dysfunction and non-ST-segment elevation acute coronary syndrome (NSTEACS). Both trial arms received aspirin (75-325 mg/day).[334]

Three cohort studies investigated the effect of prescription of aspirin compared with non-prescription of aspirin on mortality in people with CKD and heart failure (HF) and coronary artery disease (CAD) (N=6427, 1 year follow-up)[197] or in people with acute MI and CKD (N=1342, 9.8 months follow-up)[358] or in people with ACS and CKD (N=5549, 2 year follow-up).[336]

One cohort study investigated the effect of non-prescription of any antiplatelet agent (aspirin, clopidogrel, dipyridamole, or ticlopidine) on mortality within 6 months of hospital discharge in men with CKD undergoing coronary artery bypass grafting (CABG) (N=19,411).[226]

Renal function assessment was limited to one measurement of serum creatinine upon hospital admission in all of the cohort studies. The cohort studies are also limited by lack of data on treatment adherence.

The effect of antiplatelet agents on mortality, cardiovascular events, and adverse events in people with CKD and various baseline cardiovascular comorbidities is summarised in Table 214, at the end of the evidence statements.

P.10.3.3 Section 10.3.3: Health economics methodology

There were no health economics papers found to review.

P.10.3.4 Section 10.3.4: Evidence statements

All-cause mortality: clopidogrel versus placebo

In people with NSTEACS and either GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS difference in mortality for clopidogrel compared with placebo (both groups received aspirin).[334] (Level 1+)

Aspirin versus non-prescription of aspirin

Two cohort studies of people discharged from hospital following acute MI[358] or ACS[336] showed that aspirin use was NS associated with death in people with mild (GFR 60–80 ml/min/1.73m^2) or moderate (GFR 30–59 ml/min/1.73m^2) CKD. In people with ACS and GFR <30 ml/min/1.73m^2, aspirin use was associated with a significantly increased risk of death.[336] In people with acute MI and GFR 15–29 ml/min, aspirin significantly reduced mortality.[358] (Level 2+)

In another cohort with renal disease, HF, and CAD, use of aspirin significantly reduced 1-year mortality in people with CrCl 30–59 ml/min compared with non-use of aspirin. The risk of death was NS different between people with CrCl <30 ml/min + HF + CAD for aspirin compared with non-use of aspirin.[197] (Level 2+)

Non-prescription of antiplatelet drugs (aspirin, clopidogrel, dipyridamole, or ticlopidine)

Non-prescription of antiplatelet agents was associated with significantly increased odds of mortality in men with GFR <60 ml/min + CABG.[226] (Level 2+)

Cardiovascular death: clopidogrel versus placebo

In people with NSTEACS and GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS difference in cardiovascular mortality for clopidogrel compared with placebo.[334] (Level 1+)

Cardiovascular death, non-fatal MI, or stroke: clopidogrel versus placebo

Clopidogrel significantly decreased the risk of cardiovascular death, non-fatal MI, or stroke in people with GFR 64–81.2 ml/min + NSTEACS. Clopidogrel did NS reduce this outcome in people with GFR <64 ml/min.[334] (Level 1+)

Bleeding: clopidogrel versus placebo

In people with NSTEACS and GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS risk of either life-threatening or major bleeding for clopidogrel compared with placebo. However, clopidogrel use was associated with a significantly increased risk of minor bleeds.[334] (Level 1+)

Table 214: The effect of antiplatelet agents on mortality, cardiovascular events, and adverse events in people with CKD and various cardiovascular comorbidities (95% CI)

Reference	Comparison	Population	N	Outcome	Effect size
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	All-cause mortality	RR 0.95 (0.78-1.16) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	All-cause mortality	RR 0.91 (0.68-1.21) NS
[336]	Aspirin use at hospital discharge	GFR <30 ml/min/1.73m^2 + ACS	306	All-cause mortality	HR 1.232 (1.024-1.117), p not stated
[336]	Aspirin use at hospital discharge	GFR 30-59 ml/min/1.73m^2 + ACS	1795	All-cause mortality	HR 1.029 (0.988-1.081) NS
[336]	Aspirin use at hospital discharge	GFR 60-80 ml/min/1.73m^2 + ACS	2018	All-cause mortality	HR 0.851 (0.921-1.128) NS
[358]	Aspirin versus no cardioprotective agents* at hospital discharge	GFR 15-29 ml/min/1.73m^2 + MI	70	All-cause mortality	HR 0.21 (0.08-0.53), p not stated
[358]	Aspirin versus no cardioprotective agents* at hospital discharge	GFR 30-59 ml/min/1.73m^2 + MI	412	All-cause mortality	HR 0.65 (0.37-1.12) NS
[358]	Aspirin versus no cardioprotective agents* at	GFR 60-89 ml/min/1.73m^2 + MI	612	All-cause mortality	HR 0.97 (0.50-1.86) NS

Reference	Comparison	Population	N	Outcome	Effect size
	hospital discharge				
[197]	Aspirin versus no aspirin at hospital discharge	CrCl < 30 ml/min + HF + CAD	466	1 year All-cause mortality	HR 0.84 (0.64-1.11) NS
[197]	Aspirin versus no aspirin at hospital discharge	CrCl 30-59 ml/min + HF + CAD	2047	1 year All-cause mortality	HR 0.81 (0.67-0.98), p not given
[226]	Non-prescription of antiplatelet drugs** within 6 months of hospital discharge	GFR <60 ml/min + CABG	3260	All-cause mortality within 6 months of hospital discharge	OR 1.90 (1.23-2.94), p=0.004
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	Cardiovascular death, non-fatal MI, or stroke	RR 0.89 (0.76-1.05) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	Cardiovascular death, non-fatal MI, or stroke	RR 0.68 (0.56-0.84) p <0.05
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	Cardiovascular Death	RR 0.95 (0.77-1.17) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	Cardiovascular Death	RR 0.85 (0.63-1.16) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	Life-threatening bleed	RR 0.89 (0.60-1.31) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	Life-threatening bleed	RR 1.23 (0.78-1.93) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	Major bleed	RR 1.37 (0.89-2.12) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	Major bleed	RR 1.78 (0.95-3.34) NS
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4087	Minor bleed	RR 1.50 (1.21-1.86), p <0.05
[334]	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64-81.2 ml/min + NSTEACS	4075	Minor Bleed	RR 1.61 (1.27-2.06), p <0.05

**Cardioprotective agent = aspirin, beta-blocker, or ACEI.*

***Antiplatelet agents = aspirin, clopidogrel, dipyridamole or ticlopidine.*

P.10.3.5 Section 10.3.5: From evidence to recommendations

Interpretation of the results of observational studies of the impact of aspirin may be confounded by the indications for aspirin prescription. The study participants had varying levels of kidney function and follow up was relatively short.

Use of aspirin was associated with a reduction in mortality in people with a GFR below 60 ml/min/1.73m^2 who had had a myocardial infarction.

The GDG agreed that there was no reason to believe that antiplatelet drugs were less effective for secondary prevention of cardiovascular events in people with CKD.

People with CKD are at increased risk of bleeding and this risk is increased by the use of one or more antiplatelet drugs. The evidence does not show a significant increase in the incidence of major bleeding but there is an increased risk of minor bleeding.

P.10.3.6 Section 10.3.6: RECOMMENDATION

R59 Offer antiplatelet drugs to people with CKD for the secondary prevention of CVD. CKD is not a contraindication to the use of low dose aspirin but clinicians should be aware of the increased risk of minor bleeding in people with CKD given multiple antiplatelet drugs.

P.11 Section 11: Asymptomatic hyperuricaemia

P.11.1 Section 11.1: Asymptomatic hyperuricaemia in people with CKD

P.11.1.1 Section 11.1.1: Clinical introduction

Uric acid is a product of purine metabolism. After glomerular filtration, uric acid is both reabsorbed and excreted in the proximal tubule. Hyperuricaemia may result from either increased production or decreased excretion of uric acid. Increased production may occur through enzyme defects, increased purine turnover (myeloproliferative disorders and certain forms of cancer), or from increased consumption in diet. In patients with renal disease there is decreased urinary uric acid excretion. Whether this gives rise to hyperuricaemia depends on the degree of gastrointestinal excretory compensation.[698] It has been shown that increasing levels of uric acid are associated with significantly increased hazard ratios for CKD, but the associations with progressive CKD are less strong.[120,204]

There is theoretical evidence to support the role for uric acid as both an initiator of CKD, and a factor involved in its progression. It has been proposed that an elevated uric acid may have a role in initiating hypertension, arteriolosclerosis, kidney disease, insulin resistance, and hypertriglyceridaemia. Once renal microvascular disease develops, the kidney will drive hypertension; once obesity develops fat-laden adipocytes will contribute to insulin resistance, and once kidney disease develops the kidney will also drive progression.[465]

Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. Experimental rat models have suggested that allopurinol treatment can prevent hyperuricaemia-induced functional and structural injury of the kidney. In animal models of established renal diseases, correction of the hyperuricemic state can significantly improve blood pressure control, decrease proteinuria, and decrease the amount of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy.[320,466,603]

Does lowering uric acid with (a) allopurinol, (b) uricosuric agents (probenecid, sulfinpyrazone), (c) rasburicase (urate oxidase), decrease morbidity and mortality in adults with CKD and hyperuricaemia?

P.11.1.2 Section 11.1.2: Methodology

In non-CKD populations, treatment of hyperuricaemia is only indicated if the patient has symptomatic arthritis. The literature was reviewed to determine if treatment with allopurinol, probenecid, sulfinpyrazone, or rasburicase decreases progression of CKD and mortality in people with CKD and hyperuricaemia. There was little evidence in this area. There were no studies assessing rasburicase, probenecid, or sulfinpyrazone in people with pre-dialysis CKD.

Only one open label RCT[638] compared 12 months of allopurinol treatment (100–200 mg/day dose, N=25) with usual treatment (N=26) in adults (mean age 48 years) with CKD and hyperuricaemia. Both trial arms received lipid lowering and antihypertensive agents throughout the study. This study was excluded as it had several methodological limitations. It was a small study, open-labelled, did not present intention to treat analysis, and did not provide statistical power calculations. There was little information on what treatments the 'usual treatment' group received. It may be also be difficult to extrapolate the findings from this study to a UK population as it was conducted in a Chinese population.

P.11.1.3 Section 11.1.3: Health economics methodology

There were no health economics papers found to review.

P.11.1.4 Section 11.1.4: Evidence statements

There are no evidence statements.

P.11.1.5 Section 11.1.5: From evidence to recommendation

The GDG agreed that there was no evidence to support treatment of asymptomatic hyperuricaemia in people with CKD.

P.11.1.6 Section 11.1.6: RECOMMENDATION

R60 There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia.

P.12 Section 12: Managing isolated invisible haematuria

P.12.1 Section 12.1: Isolated invisible (microscopic) haematuria

P.12.1.1 Section 12.1.6: RECOMMENDATIONS

R61 When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, regard two out of three positive reagent strip tests as confirmation of persistent invisible haematuria.

R62 Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups.

R63 Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria/albuminuria, glomerular filtration rate (GFR) and blood pressure monitoring as long as the haematuria persists.

P.13 Section 13: Specific complications of CKD – renal bone disease

P.13.1 Section 13.1: Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD

P.13.1.1 Section 13.1.6: Recommendations

R64 The routine measurement of calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with stage 1, 2, 3A or 3B CKD is not recommended.

R65 Measure serum calcium, phosphate and PTH concentrations in people with stage 4 or 5 CKD (glomerular filtration rate (GFR) <30 ml/min/1.73m^2). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists seek specialist opinion.

P.13.2 Section 13.2: Risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD

P.13.2.1 Section 13.2.6: RECOMMENDATIONS

R66 Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with CKD stage 1, 2, 3A or 3B.

P.13.3 Section 13.3: Vitamin D supplementation in people with CKD

P.13.3.1 Section 13.3.1: Clinical introduction

Vitamin D is normally either ingested or synthesised in the skin under the influence of sunlight. It is then hydroxylated in the liver to form 25-hydroxyvitamin D (calcidiol) and then hydroxylated in the kidney to 1,25-dihydroxyvitamin D (calcitriol), which is the most active form. Vitamin D deficiency can therefore occur as a result of decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, or decreased endogenous synthesis (via 25-hydroxylation in the liver and subsequent 1-hydroxylation in the kidney). Active vitamin D has a variety of actions on calcium, phosphate, and bone metabolism. By increasing intestinal calcium and phosphate reabsorption and increasing the effect of parathyroid hormone (PTH) on bone, in health vitamin D has the net effect of increasing the serum calcium and phosphate concentrations. Vitamin D deficiency or resistance interferes with these processes, sometimes causing hypocalcaemia and hypophosphataemia. Since hypocalcaemia stimulates the release of PTH, however, the development of hypocalcaemia is often masked. The secondary hyperparathyroidism, via its actions on bone and the kidney, partially corrects the hypocalcaemia but enhances urinary phosphate excretion, thereby contributing to the

development of hypophosphataemia. In people with CKD the kidney component of this loop is increasingly compromised as CKD advances.

As renal function declines, the hydroxylating activity of renal 1α-hydroxylase on 25-hydroxyvitamin D3 also decreases, resulting in decreased production of active vitamin D (1,25-dihydroxyvitamin D3) and decreased intestinal absorption of calcium. The decrease in calcium and active vitamin D3 alleviates the repression of parathyroid hormone (PTH) production, resulting in hyperproliferation of parathyroid cells. High PTH levels cause an increase in bone remodelling, leading to high bone-turnover (osteitis fibrosa), loss of bone density and structure. This excess bone remodelling liberates calcium and phosphorus from bone, resulting in hypercalcaemia and hyperphosphataemia and increasing the risk for vascular calcification.

Vitamin D supplementation in people with CKD should therefore be driven by the underlying metabolic abnormality. This in turn will depend on the stage of CKD but is complicated by the fact that in the population with the highest prevalence of CKD, the older population, vitamin D deficiency is common. Cutaneous vitamin D production and vitamin D stores decline with age coupled with the fact that intake is often low in older subjects. Furthermore, even in those with adequate vitamin D intake, achlorhydria, which is common in older people, limits vitamin D absorption. Nutritional forms of vitamin D include ergocalciferol and cholecalciferol, active forms of vitamin D include alfacalcidol, calcitriol and paricalcitol. Elderly patients are likely to be vitamin D deficient from diet, lack of sunlight and poor absorption for which they will need nutritional vitamin D, however as CKD progresses (particularly in stages 4 and 5) renal function is impaired to such a degree that active vitamin D may also be required.

What type of vitamin D supplementation, if any, should be used in adults with CKD?

P.13.3.2 Section 13.3.2: Methodology

Eight RCTs and one case series investigated the safety and efficacy of various natural and synthetic vitamin D metabolites to treat secondary hyperparathyroidism and to prevent bone loss in people with pre-dialysis CKD. Outcomes of interest included adverse events, fractures, changes in serum calcium, phosphorus, PTH, osteocalcin, alkaline phosphatase, GFR, and bone mineral density. All of these studies are limited by small sample sizes (N=25–220), and very few presented intention to treat analyses. There were no studies of acceptable methodological quality that compared different vitamin D metabolites head-to-head.

Four RCTs[51,490,557,572]pr compared calcitriol supplementation to placebo in people with CKD. Two of these RCTs titrated the dose of calcitriol from 0.25 µg/day up to 0.5 µg/day.[51,490] In the RCT of Przedlacki et al., treatment with calcitriol (0.25 µg/day, N=13, 12 months follow-up) was compared with placebo (N=12) in people with eGFR < 51.2 ml/min. In the RCT of Ritz et al., a low dose of calcitriol (0.125 µg/day, N=28, follow-up 1 year) was compared with placebo (N=24) in people with nondiabetic CKD and abnormal iPTH levels (iPTH >6 pmol/l on 3 separate occasions). The Baker et al. study (N=13, follow-up 12 months) was excluded due to small sample size, high dropout rate, and lack of baseline data comparison between the two trial arms.

One RCT compared 6 months of treatment with calcitrol (N=8, 1 µg/day) or calcidiol (N=9, 4000 IU/day) in people with chronic renal failure.[122] This study was rejected because there was no

indication of blinding, concealment, intention to treat, and statistical power to detect differences between the two groups.

Two RCTs investigated the effects of treatment with alfacalcidol (1-α-hydroxycholecalciferol) compared to placebo in people with mild to moderate CKD (creatinine clearance 10-60 ml/min).[245,573] The Hamdy et al. RCT (N=89 alfacalcidol and N=87 placebo, 24 months follow-up) titrated the dose of alfacalcidol from 0.25 to 1 µg/day. Most of the participants had abnormal bone histology at baseline (NS difference between the trial arms). The smaller RCT of Rix et al. (N=36, 18 months follow-up) titrated alfacalcidol from 0.25 to 0.75 µg/day.

A pooled analysis of 3 RCTs with identical inclusion/exclusion criteria and different dosing regimens (3 times weekly or once daily) compared paricalcitol (N=107, 6 months follow-up, mean dose was 1.3 to 1.4 µg/day) with placebo (N=113) in people with CKD and hyperparathyroidism (iPTH ≥ 150 pg/ml). Although this study was not a systematic review, it was included as an RCT (albeit pooled) due to lack of studies of non-dialysis CKD populations.[143]

One retrospective case series examined changes in serum calcium, phosphate, iPTH, and adverse events before and after 6 months' treatment with ergocalciferol (vitamin D2) in men with stage 3 CKD and plasma iPTH >70 ng/l (N=44) or stage 4 CKD and plasma iPTH >110 ng/l (N=22).[25]

P.13.3.3 Section 13.3.3: Health economics methodology

There were no health economics papers found to review.

P.13.3.4 Section 13.3.4: Evidence statements

Calcitrol versus placebo

Refer to Table 215 for summary of studies.

Serum calcium

One RCT showed that serum calcium significantly increased with calcitrol (0.25 titrated to 0.5 µg/day) compared with placebo.[490] (Level 1+)

Two RCTs showed NS changes in mean serum calcium in people taking calcitrol (0.25 µg/day steady or 0.125 µg/day) or placebo.[557,572] (Level 1 +)

Serum phosphorus

Three RCTs showed that mean serum phosphate did NS change in either the placebo or calcitrol groups.[490,557,572] (Level 1 +)

Serum parathyroid hormone (PTH)

Two RCTs showed that iPTH significantly decreased in people receiving calcitrol, whereas in the placebo groups, iPTH levels either increased significantly[490] or did not significantly change.[557] (Level 1 +)

One RCT showed that iPTH decreased from baseline in the calcitrol group whereas iPTH increased from baseline in those taking placebo ($p<0.05$ between placebo and calcitrol groups).[572] (Level 1 +)

Serum alkaline phosphatase (ALP)

Two RCTs showed that serum ALP decreased significantly in people taking calcitrol, whereas there were NS changes in ALP in people taking placebo.[490,557] (Level 1 +)

Serum osteocalcin

One RCT showed that mean serum osteocalcin significantly decreased in the calcitrol group, whereas osteocalcin significantly increased in the placebo group.[557] (Level 1 +)

Change in eGFR or creatinine clearance

Two RCTs showed that creatinine clearance or GFR significantly decreased in both the calcitrol and the placebo groups, but there were NS differences between the groups.[490,557] (Level 1)

Bone mineral density (BMD)

BMD of the lumbar spine (L2–L4), femoral neck, and trochanter significantly increased in the calcitrol group. By contrast BMD of the lumbar spine (L2–L4), femoral neck, and trochanter significantly decreased in the placebo group ($p<0.01$ between groups).[557] (Level 1+)

Indices of bone formation, remodelling and structure

There were NS changes in bone volume in placebo or calcitrol groups.[490] (Level 1+)

Indices of bone formation, remodelling and structure (osteoid volume, osteoid thickness, osteoid surface, eroded surface, osteoclast surface, bone formation rate, mineralisation surface, and mineral apposition rate, singly labelled trabecular surfaces) significantly decreased in the calcitrol group, whereas there were NS changes in the placebo group.[490] (Level 1+)

There were NS changes in doubly labelled trabecular surfaces in calcitrol or placebo groups. (Level 1+)

Adverse events

Hypercalcaemia (>2.6 mmol/l) was observed in 2/13 people receiving calcitrol and 0/12 receiving placebo. Hyperionised calcaemia (blood ionised Ca >1.29 mmol/l) occurred in 5/13 on calcitrol and 3/12 in the placebo group.[557]

There was no hypercalcaemia (>2.7 mmol/l on three consecutive occasions) in either calcitrol (0.125 µg/day) or placebo groups.[572]

There was no hyperphosphataemia (>2.2 mmol/l on 3 consecutive occasions) in either calcitrol (0.125 µg/day) or placebo groups.[572]

Hyperphosphataemia (P >1.5 mmol/l) occurred in 3/12 placebo and 10/13 randomised to calcitrol (NS between groups).[557] (Level 1+)

Table 215: Summary of studies comparing calcitriol with placebo

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
[490]	Creatinine > 180 µmol/l and stable renal function	8	14	14	Change iPTH (µg/l)	Calcitriol 1.33 → 0.98 (-26%), p <0.01 Placebo 0.94 → 1.37, (+ 46%), p <0.01
[557]	GFR <51.2 ml/min	12	13	12	Change iPTH (ng/l)	calcitriol 150 → 105.8 (-29%), p <0.05 Placebo 122.6 → 151.4, (+23%) p NS
[572]	Creatinine >1.4 mg/dl and <6.5 mg/dl and iPTH >6 pmol/l	12	28	24	Change iPTH (pmol/l)	Calcitriol 16.2 →18.2, p not given Placebo 14.0 → 27.8 p <0.05 between treatments
[557]	GFR <51.2 ml/min	12	13	12	Change Osteocalcin (µmol/l)	Calcitriol 26.3 → 20.0 (-24%), p <0.05 Placebo 24.6 → 28.3 (+15%) p <0.05
[490]	Creatinine >180 µmol/l and stable renal function	8	14	14	Change Serum alkaline phosphatase (U/l)	Calcitriol: 201 → 155 (-23%), p<0.05 Placebo: 209 → 200 (-4%) NS. p <0.05 for between groups
[557]	GFR <51.2 ml/min,	12	13	12	Change Serum alkaline phosphatase (U/l)	Calcitriol: 165.0 →143, p <0.05). Placebo: NS
[490]	Creatinine >180 µmol/l and stable renal function	8	15	15	Change in CrCl	Calcitriol: -5ml/min (approx.), p <0.01 Placebo: -5ml/min (approx.), p <0.01 NS between groups
[557]	GFR <51.2 ml/min	12	13	12	Change in	Calcitriol: 21.5

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
					GFR	ml/min → 18.7 ml/min, p <0.05) Placebo: 31.3 ml/min →26.3 ml/min, p <0.05 NS between treatments.
[557]	GFR <51.2 ml/min,	12	13	12	Change Bone Mineral Density (g/cm^2)	Calcitriol lumbar spine: 1.111 →1.133, p <0.001 Placebo lumbar spine: 1.214 → 1.201, p <0.05 p <0.01 between groups Calcitriol femoral neck 0.806 → 0.832, p <0.001. Placebo femoral neck 0.860 → 0.845, p <0.05 p <0.001 between groups. Calcitriol: Ward's triangle NS Placebo: Ward's triangle 0.720 → 0.702, p<0.05 Calcitriol: trochanter 0.708 →0.724, p<0.05 Placebo: trochanter 0.800 → 0.783, p<0.05

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
[490]	Creatinine > 180 µmol/l and stable renal function	8	14	14	Change Bone volume	NS change placebo or calcitriol.
					Change Osteoid volume	calcitriol: 5% →3%, p<0.01 Placebo: 8% → 6%, NS p <0.01 between groups
					Change Osteoid thickness (µm)	calcitriol: 9.6 → 6.1, p <0.01) placebo : 9.0 → 10, NS
					Change Osteoid surface	Calcitriol decreased, p <0.05 Placebo: NS change p <0.01 between groups
					Change Eroded surface	Calcitriol decreased, p <0.05 Placebo: NS change p <0.05 between groups
					Change Osteoclast surface	Calcitriol decreased, p <0.01 Placebo: NS change p <0.01 between groups
					Change Bone formation rate	Calcitriol: decreased, p <0.01 Placebo: NS change p <0.05 between groups

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
					Change Mineral apposition rate (µm/day)	Calcitriol: 0.53 → 0.44, p <0.05. Placebo: 0.55 →0.50, NS

Alfacalcidol (1α-hydroxycholecalciferol) versus placebo

Refer to Table 216 at the end of the evidence statements for a summary of studies.

Serum calcium

Two RCTs showed that mean serum calcium increased significantly in people taking alfacalcidol, while there were NS changes in calcium in people taking placebo, p <0.001 between groups.[245,573] (Level 1 +)

Serum phosphorus

Two RCTs showed that there were NS changes in serum P in the alfacalcidol or placebo groups.[245,573] (Level 1+)

Serum parathyroid hormone (PTH)

The RCT of Hamdy et al. showed a NS decrease in iPTH with alfacalcidol treatment and a significant increase in iPTH in the placebo group. At 24 months, iPTH returned to baseline levels in those with alfacalcidol treatment. (Level 1+)

The RCT of Rix et al. showed a significant decrease in iPTH with treatment with alfacalcidol, whereas there were NS changes in iPTH in the placebo group, p <0.05 between groups. (Level 1+)

Serum alkaline phosphatase (ALP)

Bone-specific ALP significantly decreased in the alfacalcidol group, whereas there was NS change in ALP in the placebo group.[573] (Level 1+)

Serum osteocalcin

Osteocalcin significantly decreased in the alfacalcidol group, whereas there was NS change in osteocalcin in the placebo group. At the end of the study only 1 person in the alfacalcidol group had osteocalcin levels above the reference range (4.2–31.4 ng/ml), whereas 6 people in the placebo group had osteocalcin levels exceeding reference ranges.[573] (Level 1+)

Change in creatinine clearance

Two RCTs showed that CrCl decreased significantly in both placebo and alfacalcidol groups, but there were NS differences between treatments.[245,573] (Level 1+)

Bone mineral density (BMD)

There was a significant difference for BMD of the spine in the alfacalcidol versus placebo group (4.2%, p <0.05).[573] (Level 1+)

There was a significant difference for BMD of the femoral neck in the alfacalcidol versus placebo group (4.9%, p <0.05).[573] (Level 1+)

There were NS changes in total body BMD or forearm BMD in the placebo or the alfacalcidol groups.[573] (Level 1+)

Indices of bone formation, remodelling and structure

In people with histological bone abnormalities at baseline (N=100), there were NS differences in bone volume in the placebo (N=45) or alfacalcidol (N=55). (Level 1+)

Osteomalacia improved in people taking alfacalcidol as the number of osteoid lamellae decreased whereas the number of osteoid lamellae increased in the placebo group, p=0.002 between groups. (Level 1+)

The proportion of people with bone abnormalities at the beginning of the study was similar between the placebo (73%) and alfacalcidol (76%) groups. After 24 months treatment, 54% of people taking alfacalcidol and 82% on placebo had bone abnormalities (no p given). (Level 1+)

Fibrosis significantly decreased in people taking alfacalcidol, while fibrosis increased in the placebo group, p=0.0002 between groups. (Level 1+)

Osteoid volume, osteoid surface, osteoblast surface, and osteoclast surface all decreased significantly in the alfacalcidol group, whereas there were NS changes in any of these parameters in the placebo group, p <0.05 between groups for each outcome. (Level 1+)

There were NS differences in mineral apposition rate between placebo or alfacalcidol groups. (Level 1+)

Bone formation rate decreased significantly in alfacalcidol group, but there was NS change in placebo and NS difference between groups. (Level 1+)

Bone resorption decreased in people taking alfacalcidol compared with placebo. The eroded bone surface significantly decreased in the alfacalcidol group while it increased in the placebo group, p=0.04 between groups. Also, alfacalcidol was associated with a significant decrease of active eroded surface compared with placebo, p=0.0006 between groups.[245] (Level 1+)

Adverse events

Mild hypercalcaemia (>2.63 mmol/l on 2 occasions) was seen in 10/89 patients receiving alfacalcidol and 3/87 patients receiving placebo (p=0.09, NS). Severe hypercalcaemia (>3.00 mmol/l on 1 occasion) was observed in 4 people taking alfacalcidol and 0 people on placebo.[245] (Level 1+)

Hypercalcaemia occurred in 1/18 people on alfacalidol.[573] (Level 1+)

Mild GI disturbances were reported in 6/89 people on alfacalcidol and 1/87 on placebo.[245] (Level 1+)

Pseudogout was reported by 2/89 people on alfacalcidol.[245,245] (Level 1+)

Table 216: Summary of studies comparing alfacalcidol with placebo

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
[245]	CrCl 15-50 ml/min, 75% had bone abnormalities	24	89	87	Change iPTH (pmol/l)	Alfacalcidol: -1.6 pmol/l, NS Placebo +7.3 pmol/l, p <0.001
[573]	CrCl 10-60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change iPTH (%)	Alfacalcidol: -47% , p <0.05 Placebo NS p <0.05 between groups
[573]	CrCl 10-60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change osteocalcin (%)	Alfacalcidol: -24%, p <0.05 Placebo: + 25%, NS p <0.05 between groups
[573]	CrCl 10-60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change bone-specific alkaline phosphatase (%)	Alfacalcidol: -48% p <0.05 Placebo: NS
[245]	CrCl 15-50 ml/min, 75% had bone abnormalities	24	89	87	Change in CrCl:	Alfacalcidol : -5.7ml/min, Placebo: -4.0 ml/min NS between treatments
[573]	CrCl 10-60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change in CrCl:	Decreased significantly in both placebo and alfacalcidol groups,

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
						NS between treatments.
[573]	CrCl 10-60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change Bone Mineral Density	Alfacalcidol spine: +2.9% NS Placebo spine: -1.1% change, NS Alfacalcidol versus placebo group (4.2%, p <0.05). Alfacalcidol femoral neck : +1.5%, NS Placebo femoral neck: -1.5%, NS Alfacalcidol versus placebo group (4.9%, p <0.05). NS changes in total body BMD in the placebo or the alfacalcidol NS changes in forearm BMD in the placebo or the alfacalcidol groups
[245]	CrCl 15-50 ml/min, 75% had bone abnormalities	24	55	45	Change Bone volume	Alfacalcidol: 1.22 Placebo: 1.09 p=0.75 between groups
		24	55	45	Change Osteoid volume	Alfacalcidol : -0.30, p <0.01 Placebo: 0.09, NS

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
						p=0.005 between groups
		24	55	45	Change Osteoid surface	Alfacalcidol: -6.85, p<0.01 Placebo: +1.35, NS p=0.008 between groups
		24	55	45	Change Eroded surface	Alfacalcidol : -3.76 Placebo : +0.45 p=0.04 between groups
		24	55	45	Change Osteoclast surface	Alfacalcidol: -0.30, NS) NS Placebo: +0.17 p=0.002 between groups
		24	55	45	Change Bone formation rate	Alfacalcidol: -4.66, p <0.05 Placebo: +0.51, p=0.15 NS between groups
		24	55	45	Change Mineral apposition rate (µm/day)	NS changes in alfacalcidol or placebo and NS between groups (p=0.34)

Paricalcitol versus placebo

Refer to Table 217 for a summary of studies.

Serum calcium

Mean serum calcium increased slightly in people taking paricalcitol, while there were small decreases in serum calcium in the placebo group, NS between groups.[143] (Level 1+)

Serum phosphorus

There were NS changes in serum phosphate in the paricalcitol or placebo groups.[143] (Level 1 +)

Serum parathyroid hormone (PTH)

Serum iPTH decreased significantly from baseline to 6 months treatment with paricalcitol, whereas iPTH increased in the placebo group (p<0.001 between groups).[143] (Level 1+)

Serum alkaline phosphatase (ALP)

Bone-specific ALP significantly decreased from baseline to 6 months in the paricalcitol group, compared with a smaller decrease in bone ALP in the placebo group, p <0.001 between groups.[143] (Level 1+)

Serum osteocalcin

Serum osteocalcin significantly decreased in the paricalcitol group, compared with an increase in osteocalcin in the placebo group (p <0.001 between groups).[143] (Level 1+)

Change in GFR

After 6 months, eGFR decreased in both placebo and paricalcitol groups, but there were NS differences between treatments.[143] (Level 1+)

Two consecutive reductions in iPTH ≥ 30% from baseline

Significantly more people taking paricalcitol achieved 2 consecutive ≥30% decreases in serum iPTH from baseline compared with people taking placebo (p <0.001 between groups). Significantly more people taking paricalcitol achieved iPTH <110 ng/l compared with those on placebo.[143] (Level 1+)

Four consecutive reductions in iPTH ≥ 30% from baseline

Significantly more people taking paricalcitol achieved 4 consecutive ≥30% decreases in serum iPTH from baseline compared with the placebo group (p <0.001 between groups).[143] (Level 1+)

Urinary deoxypryidinoline

There were NS differences between paricalcitol or placebo groups for changes in urinary deoxypryidinoline.[143] (Level 1+)

Urinary pyridinoline

Urinary pyridinoline decreased significantly in the paricalcitol group, compared with an increase in the placebo group (p=0.006 between groups).[143] (Level 1+)

Adverse events

Hypercalcaemia (2 consecutive Ca >2.62 mmol/l) occurred in 2 people on paricalcitol and no people on placebo (NS).

Hyperphosphataemia (2 consecutive PO4 >1.78 mmol/l) occurred in 11 people on paricalcitol and 13 people on placebo (NS).[143] (Level 1+)

Table 217: Summary of studies comparing paricalcitol versus placebo

Study	Population	Duration (months)	Paricalcitol (N)	Placebo (N)	Outcome	Size effect
[143]	3 pooled RCTs: CKD, iPTH ≥150 pg/ml, Ca 1.99-2.40 mmol/l and PO4 ≤1.68 mmol/l.	6	101	108	Change iPTH (%)	Paricalcitol: - 45.2% (max) Placebo: +13.9% (max) p <0.001 between groups
			101	108	2 consecutive decreases ≥30% of iPTH	Paricalcitol: 91% Placebo : 13% p <0.001 between groups
			100	104	Change osteocalcin, ng/ml	Paricalcitol: -21.6 ng/ml Placebo: +10.7 ng/ml p <0.001 between groups
			101	107	Change Bone-specific alkaline phosphatase (□g/l)	Paricalcitol : -7.89 µg/l Placebo: -1.44 µg/l, p <0.001 between groups
			82	93	Change in GFR:	Paricalcitol: -2.52 ml/min/1.73m^2, (-10.4%) placebo : -1.57 ml/min/1.73m^2 (-6.95%) NS between treatments.

Before versus after treatment with ergocalciferol (vitamin D2)

Serum calcium

Mean serum calcium did NS change after 6 months treatment with ergocalciferol in the whole group (N=66), stage 3 CKD alone (N=44) or stage 4 CKD alone (N=22).[25] (Level 3)

Serum phosphate

Mean serum phosphate did NS change after 6 months treatment with ergocalciferol in the whole group, stage 3 CKD alone or stage 4 CKD alone.[25] (Level 3)

Serum parathyroid hormone (PTH)

In those with stage 3 CKD (N=44), iPTH significantly decreased after 6 months of ergocalciferol treatment (-22%, p <0.005). In the stage 4 CKD group (N=22) there was NS change in iPTH.[25] (Level 3)

Adverse events

There were no cases of hypercalcaemia or hyperphosphataemia before or after ergocalciferol.[25] (Level 3)

P.13.3.5 Section 13.3.5: From evidence to recommendations

The classification in the BNF[6] of the forms of vitamin D available as pharmacological supplementation can be confusing. Both preparations containing ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are listed under the heading 'ergocalciferol'.

Tablets of ergocalciferol combined with calcium are the cheapest form of vitamin D, but preparations of cholecalciferol combined with calcium are also cheaper than alfacalcidol and calcitriol. The GDG observed that cholecalciferol is the most commonly prescribed form used to treat simple vitamin D deficiency in primary care.

The GDG noted that the costs of 1-□-hydroxyvitamin D (alfacalcidol) and 1,25-dihydroxyvitamin D (calcitrol) are very similar.

There is no evidence as to whether one form of vitamin D is more effective than another as all the studies were comparisons with placebo and there were no trials that looked at 25-hydroxyvitamin D.

The GDG noted that all forms of vitamin D will suppress PTH secretion.

It was agreed that given the similar prevalence of vitamin D deficiency in people with stage 1, 2, 3A and 3B CKD it was most likely that the deficiency was related to poor dietary intake or limited sunlight exposure. Renal hydroxylation was likely to be normal in these people. They therefore recommended that ergocalciferol or cholecalciferol should be the first treatment used to treat vitamin D deficiency in these people.

Because of reduced renal hydroxylation in people with stage 4 and 5 CKD the GDG recommended that when vitamin D supplementation was necessary in these people, it should be with the 1-□-hydroxylated or, 1,25-dihydroxylated forms.

Although no statistically significant increase in the overall frequency of hypercalcaemia was observed in people with CKD given vitamin D, severe hypercalcaemia occurred in 4 people on calcitriol versus 0 people in the placebo group in one study of calcitriol. The GDG also noted that the BNF suggests that 'all people receiving pharmacological doses of vitamin D should have the plasma calcium concentration checked at intervals (initially weekly) and whenever nausea or vomiting are present'. The GDG recommended that further research should be undertaken on the occurrence of hypercalcaemia in people with CKD treated with different vitamin D preparations.

P.13.3.6 Section 13.3.6: RECOMMENDATIONS

R67 When vitamin D supplementation is indicated in people with CKD, offer:

- cholecalciferol or ergocalciferol to people with stage 1, 2, 3A or 3B CKD

- 1-α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol) to people with stage 4 or 5 CKD.

R68 Monitor serum calcium and phosphate concentrations in people receiving 1-α-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol supplementation.[l]

P.14 Section 14: Specific complications of CKD – anaemia

P.14.1 Section 14.1: Anaemia identification in people with CKD

P.14.1.1 Section 14.1.1: Clinical introduction

NICE clinical guideline 39 ('Anaemia management in people with CKD')[473] recommended that management of anaemia should be considered in people with anaemia of CKD when their haemoglobin (Hb) level is less than or equal to 11 g/dl. The guideline was written for people with a GFR <60 ml/min/1.73m^2 already known to have a haemoglobin level ≤11 g/dl but gave no recommendations about testing for anaemia.

P.14.1.2 Section 14.1.2: RECOMMENDATION

R69 If not already measured, check the haemoglobin level in people with stage 3B, 4 and 5 CKD to identify anaemia (Hb <11.0 g/dl – see NICE clinical guideline 39: 'Anaemia management in people with chronic kidney disease'). Determine the subsequent frequency of testing by the measured value and the clinical circumstances.

P.15 Section 15: Information needs

P.15.1 Section 15.1: Information, education and support for people with CKD and their carers

P.15.1.1 Section 15.1.6: RECOMMENDATIONS

R70 Offer people with CKD education and information tailored to the stage and cause of CKD, the associated complications and the risk of progression.

R71 When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested:

- What is CKD and how does it affect people?
- What questions should people ask about their kidneys when they attend clinic?
- What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication?
- What can people do to manage and influence their own condition?
- In what ways could CKD and its treatment may affect people's daily life, social activities, work opportunities and financial situation, including benefits and allowances available?

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[l] Detailed advice concerning management of bone and mineral disorders in CKD is beyond the scope of this guideline. Where uncertainty exists seek advice from your local renal service.

- How can people cope with and adjust to CKD and what sources of psychological support are available.
- When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and pre-emptive transplantation), and the preparation required (such as having a fistula or peritoneal catheter).
- Conservative management may be considered where appropriate.

R72 Offer people with CKD high quality information or education programmes at appropriate stages of their condition to allow time for them to fully understand and make informed choices about their treatment

R73 Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning.

R74 Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support (for example, support groups, counselling or a specialist nurse).

P.15.2 Section 15.2: Available tools to aid identification and maximise effectiveness of treatment and management of CKD

Appendix Q: Deleted appendices from 2008 guideline

Q.1 Appendix A: Evidence-based clinical questions and literature searches

Table 218: Table of review questions with searching criteria for all questions reviewed for the 2008 guideline

Question ID	Question wording	Study type filters used	Databases and years
TEST 1	What is the best diagnostic test to measure renal function in routine clinical practice?	Systematic reviews, RCTs, cohort studies, diagnostic studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
TEST 4	In adults with CKD, what is the biological and analytical variability in eGFR testing and what factors (including fasting) affect it?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
TEST 3	What is the sensitivity and specificity of reagent strips for detecting protein and blood in the urine of patients?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
TEST 2	What are the benefits in terms of accuracy and cost in measuring albumin:creatinine ratio versus protein:creatinine ratio to quantify proteinuria in adults with CKD?	Systematic reviews, RCTs, observational studies, diagnostic studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
ULTRA 1	What are the indications for renal ultrasound in adults with CKD?	No filters, i.e. all study types	Medline 1966–2008 Cochrane 1800–2008 US Guidelines Clearinghouse (2007) National Electronic Library for Health (2007) National Institute of Health and Clinical

Question ID	Question wording	Study type filters used	Databases and years
			Excellence Website (2007) Health Technology Assessment Website (2007)
OUTS 1	At what level of GFR are patient outcomes significantly affected? Does this change with age or gender or ethnicity or presence/absence of proteinuria?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
IDENm 1	In adults, who should be tested for CKD?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
PROG 1	What constitutes a significant decline in GFR?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
RISK 2	Which factors are associated with progression of CKD? cardiovascular disease? acute kidney injury? obesity? smoking? urinary tract obstruction? ethnicity chronic use of NSAIDs	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
REFER 1	What are the criteria for referral to specialist care?	No filters, i.e. all study types	Medline 1966–2008 Cochrane 1800–2008 US Guidelines Clearinghouse (2007) National Electronic Library for Health (2007) National Institute of Health and Clinical Excellence Website (2007) Health Technology

Question ID	Question wording	Study type filters used	Databases and years
			Assessment Website (2007)
LIFE 1	In adults with CKD, does improving lifestyle habits decrease progression of CKD?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
DIET 1	Which dietary interventions are associated with improved renal outcomes in adults with CKD?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
BP 1	In adults with proteinuric/nonproteinuric CKD, what are the optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
HYPR 1	What are the most appropriate antihypertensive drugs to reduce the risk of progression of CKD and to decrease mortality in adults with CKD?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
MONIT 1	In adults with CKD commencing an ACE inhibitor or ARB, what parameters of renal function should be monitored and how often? (What action threshold should be used for stopping treatments with an ACE inhibitor/ARB)?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
RISK 1	In adults with CKD does the risk:benefit ratio of ACE inhibitors or ARBs change with increasing age?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
HYPR 2	In adults with proteinuric or non-proteinuric CKD, does treatment with a) spironolactone alone, b) combinations of spironolactone and ACE inhibitors, c) combinations of spironolactone and ARBs, or d) combinations of spironolactone and ACE inhibitors and ARBs decrease mortality and reduce the risk of progression of CKD compared with placebo or other antihypertensive agents?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008

Question ID	Question wording	Study type filters used	Databases and years
STAT 1	In adults with CKD and proteinuria, do statins decrease proteinuria and decrease the risk of progression of CKD compared with other treatments or placebo?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
LIPID 1	In adults with CKD and dyslipidaemia, do lipid lowering agents (statins, fibrates, fish oils) decrease cardiovascular disease risk and all-cause mortality compared with placebo or each other?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
ANTI 1	In adults with CKD, does antiplatelet and anticoagulant therapy reduce cardiovascular morbidity and mortality compared with placebo?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
URIC 1	Does lowering uric acid with a) allopurinol b) uricosuric agents (probenecid, sulfinpyrazone) c) rasburicase (urate oxidase), decrease morbidity and mortality in adults with CKD and hyperuricaemia?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
HAEM 1	What are the adverse outcomes associated with isolated microscopic haematuria and how should it be managed in adults with CKD?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
BONE 1	When should serum calcium, vitamin D, phosphate and intact parathyroid hormone levels be routinely measured in adults with CKD?	Systematic reviews, RCTs, observational studies	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
BONE 2	What are the risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
BONE 3	Which type of vitamin D supplementation, if any, should be used in CKD?	Systematic reviews, RCTs	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008
EDUC 1	What information, education, and support are needed for CKD patients and their carers to understand and cope with the diagnosis,	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008

Question ID	Question wording	Study type filters used	Databases and years
	treatment and outcome of CKD?		Cochrane1800–2008 Cinahl 1982–2008
TOOLS 1	What tools for community management are needed for GPs and primary care workers to manage CKD?	No filters, i.e. all study types	Medline 1966–2008 Embase 1980–2008 Cochrane1800–2008 Cinahl 1982–2008

NOTE: The final cut-off date for all searches was 8 February 2008.

Q.2 Appendix B: Scope of the guideline (2008)

Institute for Health and Clinical Excellence

National Institute for Health and Clinical Excellence

SCOPE

1 Guideline title

Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care.

1.1 Short title

Chronic Kidney Disease

2 Background

(a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on chronic kidney disease for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see Appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

(b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework. The NSF for Renal Services (2005) is of particular relevance to this guideline.

(c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their

individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Chronic kidney disease (CKD) implies some abnormality of kidney structure and/or function, may sometimes be progressive, and is often long-term and irreversible. In an important minority of people, CKD will develop into established renal failure (ERF), necessitating treatment by dialysis and/or a kidney transplant (collectively known as renal replacement therapy, RRT) for continued survival. For a small minority of people with significant associated comorbidity conservative management (i.e. all supportive treatment up to but not including RRT) may be more appropriate.

b) There is increasing evidence that if CKD is detected early on, the complications associated with CKD and progression to established renal failure can be delayed or even prevented through appropriate interventions. Regular testing of high-risk groups (people with diabetes, hypertension, cardiovascular disease or known kidney disease, and the elderly) can give an early indication of renal damage, thus allowing the delivery of interventions at an early stage. However, the diagnosis is often delayed or missed because of lack specific symptoms until CKD is at an advanced stage.

c) The majority of people with CKD do not progress to end stage renal failure, but they are at an increased risk of developing cardiovascular disease (CVD), and of hospitalisation and death. Factors associated with progression of CKD and with increased cardiovascular risk are similar and targeting of these risk factors may both reduce CVD in people with CKD and reduce progression of CKD to end stage renal failure.

d) The most recent Renal Registry Report (2005) shows that in 2004, the number of people in England receiving RRT was estimated as over

30,700 (620 per million population) 45% of whom have a functioning kidney transplant. Since 2000, there has been a 22% increase in the number of people receiving RRT (an average increase of 4.9% every year). Despite a wealth of literature detailing the increased hospitalisation, cost and mortality associated with late referral of people with advanced CKD to a nephrology service, late referral from both primary and secondary care is still at least as high as 30%. Late referral also precludes adequate assessment and preparation of those for whom conservative management is more appropriate.

e) Treatment with dialysis or kidney transplantation is very expensive; over 2% of the total NHS budget is spent on RRT. Significant costs and poor clinical outcomes are associated with the late referral of people with ERF needing RRT. Therefore, identification of people at earlier stages of CKD, appropriate management and earlier referral of those who would benefit from specialist renal services would lead to an increase in both economic and clinical effectiveness.

4 The guideline

a) The guideline development process is described in detail in two publications which are available from the NICE website (see 'Further information'). *The guideline development process: an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline. *Guideline development methods: information for National Collaborating Centres and guideline developers* provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see Appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) The guideline will offer best practice advice on the care of adults with a diagnosis of CKD and their referral to specialist nephrology services.

b) The guideline will cover the general management of CKD resulting from a variety of causes including:

- Diabetes
- Hypertension & cardiovascular disease
- Glomerulonephritis
- Renovascular disease
- Genetic causes
- Obstructive uropathy
- Drug-induced renal disease

4.1.2 Groups that will not be covered

a) Children (aged <16 years).

b) People receiving RRT (management of end-stage renal failure by dialysis or kidney transplant)

c) People with acute kidney injury and rapidly progressive glomerulonephritis

4.2 Healthcare setting

a) Primary and secondary NHS healthcare, including referral to tertiary care.

4.3 Clinical management

The guideline will cover:

a) Early detection / identification of people with chronic kidney disease (including diagnostic tests).

b) Management of chronic kidney disease. For example this might include management of:

- Hypertension and lipids, specific to CKD
- Proteinuria/albuminuria
- Progressive kidney disease
- Renal bone disease
- Acidosis
- Hyperuricaemia

And will incorporate

- The utility of specific pharmacological interventions
- Non-pharmacological interventions (such as dietary intervention, smoking cessation and exercise)

And will encompass

- monitoring of CKD
- Specific conditions such as diabetes

c) Timely and appropriate referral to specialist services (including criteria for referral)

d) Tools for community management of CKD.

e) Support for people/carers in diagnosis and self management of CKD through the provision of information, advice and education.

f) The guideline will be sensitive to ethnic issues

The guideline will not cover:

g) The treatment of each of the specific causes of CKD, such as glomerular and tubulointerstitial disease, or nephrotic syndrome

h) h) Management of pregnancy in women with CKD

i) i) Management of anaemia in people with CKD

4.4 Status

4.4.1 Scope

This is the consultation draft of the scope. The consultation period is 30th August to 27th September 2006.

The guideline will cross refer where appropriate to the following NICE guidance.

- Cinacelcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy' *NICE technology appraisal*. Expected date of publication January 2007.
- 'Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults'. *NICE clinical guideline no.15* (2004). Available from www.nice.org.uk/CG015
- 'Hypertension: the management of hypertension in adults in primary and secondary care'. *NICE clinical guideline no. 34* (2006). Available from www.nice.org.uk/CG034
- 'Anaemia management in people with chronic kidney disease (CKD)'. *NICE clinical guideline*. Expected date of publication September 2006.
- Type 2 diabetes: the management of type 2 diabetes (update)'. *NICE clinical guideline.* Expected date of publication February 2008.

- 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. *NICE clinical guideline*. Publication date to be confirmed.

4.4.2 Guideline

The development of the guideline recommendations will begin in October 2006.

5 Further information

Information on the guideline development process is provided in:

- *The guideline development process: an overview for stakeholders, the public and the NHS*
- *Guideline development methods: information for National Collaborating Centres and guideline developers*

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesprocess). Information on the progress of the guideline will also be available from the website.

Appendix – Referral from the Department of Health

The Department of Health asked the Institute to develop a guideline:

'To prepare a clinical guideline for the NHS in England on the early identification, early management and timely referral of adult patients with chronic kidney disease in primary and secondary care.'

Q.3 Appendix C : Cost-effectiveness analysis: Model to determine the cost effectiveness of CKD case finding among people at high risk

Q.3.1 Objectives

- To evaluate which is the most cost-effective strategy to measure renal function in routine clinical practice.
- To determine which high-risk group for CKD should be tested.

Q.3.1.1 Related clinical questions

IDEN 1 In adults who should be tested for CKD?

TEST 3 What is the sensitivity and specificity of reagent strips for detecting protein and blood in urine of patients?

TEST 1 What is the best test to measure renal function in routine clinical practice?

TEST 2 What are the benefits in terms of accuracy and cost in measuring albumin:creatinine ratio versus protein:creatinine ratio to quantify proteinuria in adults with CKD?

RISK 2 What factors are associated with progression of CKD? Which of the following are a risk factor for progression in adults with CKD?

- diabetes mellitus
- hypertension
- proteinuria/albuminuria
- cardiovascular disease
- age
- acute kidney injury
- chronic use of NSAIDs
- obesity

- smoking
- urinary tract obstruction
- ethnicity

OUTS 1 At what level of GFR are patient outcomes significantly affected? Does this change with age or gender or ethnicity or presence/absence of proteinuria?

TEST 4 In adults with CKD, what is the biological and analytical variability in GFR testing and what factors (including fasting) affect it?

Q.3.2 Methods

Q.3.2.1 Study population

The case for testing people with diabetes for CKD is already well established: NICE guidelines recommend regular testing and economic evaluations have found testing to be cost-effective.[92,282,339,472,480] Therefore we developed models for two other high-risk groups.

- **Model 1** Non-diabetic, hypertensive adults
- **Model 2** Non-diabetic, non-hypertensive adults (age ≥55)

The model was run for different age-sex groups. Other populations, such as people with a family history of ESRD, were not explicitly considered, since their epidemiology is not as well known as in people with hypertension and diabetes. However, a sensitivity analysis was conducted to determine the cost-effectiveness of testing at different levels of prevalence.

Q.3.2.2 Comparators

The GDG identified the following testing strategies:

1. **No testing strategy**
2. **Reagent 1 Strategy:** GFR + Proteinuria Reagent strip test
   a. positive strip → ACR;
   b. negative strip→ No further testing
3. **Reagent 2 Strategy**: GFR + Proteinuria Reagent strip test
   a. positive strip → ACR;
   b. negative strip→ 2nd Reagent Strip test
      i. positive 2nd strip → ACR;
      ii. negative 2nd strip → No further testing
4. **ACR strategy:** GFR + ACR

In both models the no testing strategy involved natural progression of CKD. But under the testing strategies, for true positives the progression is slowed and mortality reduced due to treatment with ACE inhibitors or ARBs.

Direct comparison of PCR with ACR in terms of diagnostic sensitivity and specificity was not possible since these two tests cannot meaningfully be compared against the same reference standard. However, a sensitivity analysis was conducted to find the level of sensitivity of PCR (relative to ACR) that would make PCR the more cost-effective strategy.

Q.3.2.3 Model structure and analytical methods

The cost-effectiveness was estimated using a decision tree (Figure 272 to Figure 275) that was constructed using TreeAge software. A Markov model (Figure 276) was plugged at the end of the decision tree to calculate the long term outcomes of the treatment received by patients diagnosed with CKD. Markov models have the advantage that they can measure outcomes, where events (such as change in CKD stage) can take place at any time over a long period of time. Such models also identify the number of events at each timepoint, which facilitates the discounting of cost and health outcomes to future values.

Two earlier models,[92,282] have evaluated early identification of CKD but not from a UK perspective (see sections 4.2.3 and 4.2.5 of the full guideline). These models have informed the development of our model.

The model follows the NICE reference case,[477] as follows. The costs were measured from the perspective of the National Health Services (NHS) and Personal Social Services (PSS). Health outcome was measured in terms of quality-adjusted-life-years (QALYs), where one QALY is equal to one year of full health. An annual discount rate of 3.5% was used for both costs and effects.

Figure 272: Decision tree arm for the 'no testing strategy'

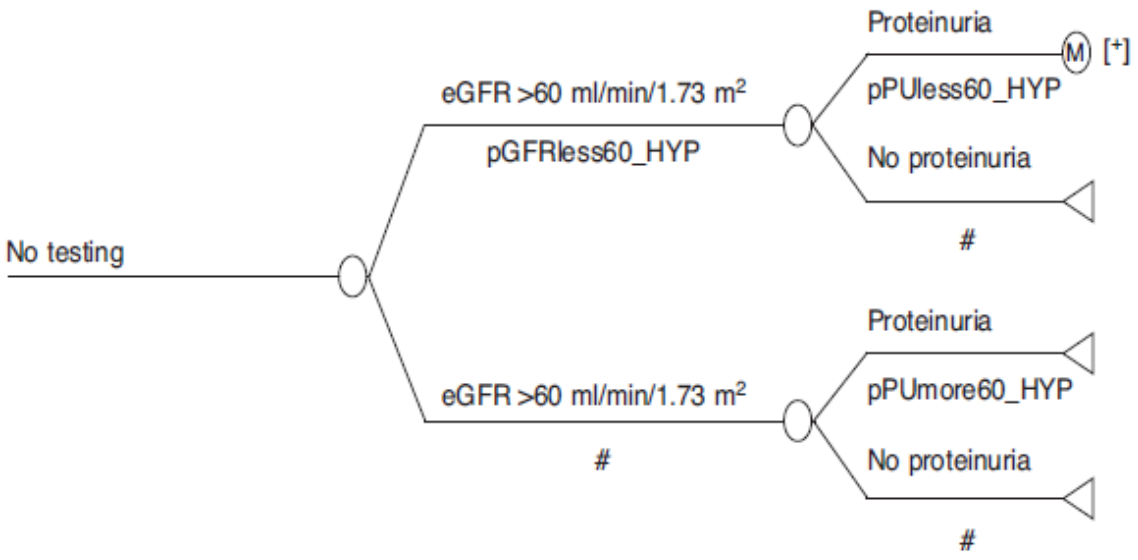


Figure 273: Decision tree arm for the 'reagent 2 strategy'

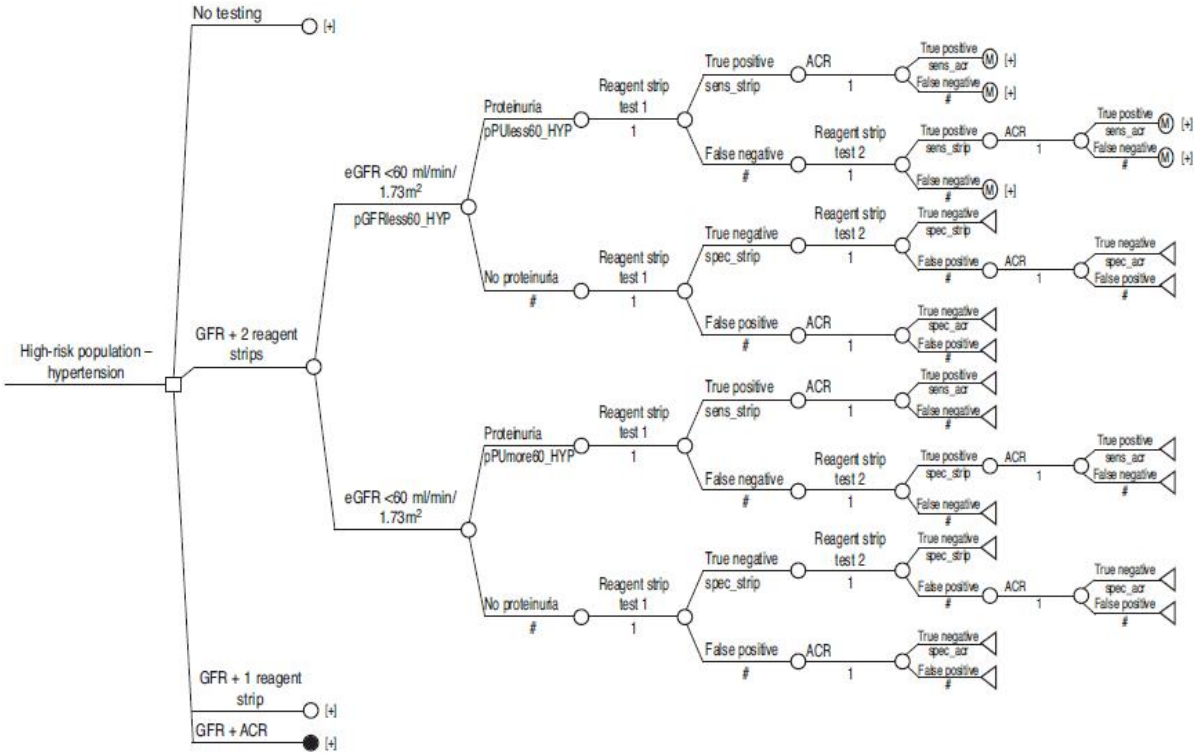


Figure 274: Decision tree arm for the 'reagent 1 strategy'

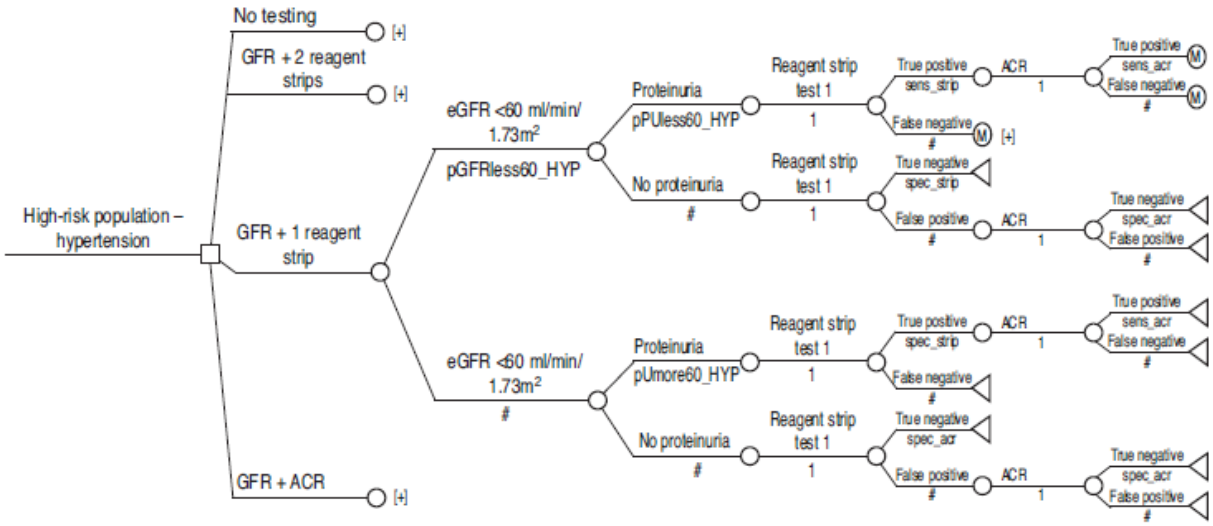


Figure 275: Decision tree arm for the 'ACR strategy'

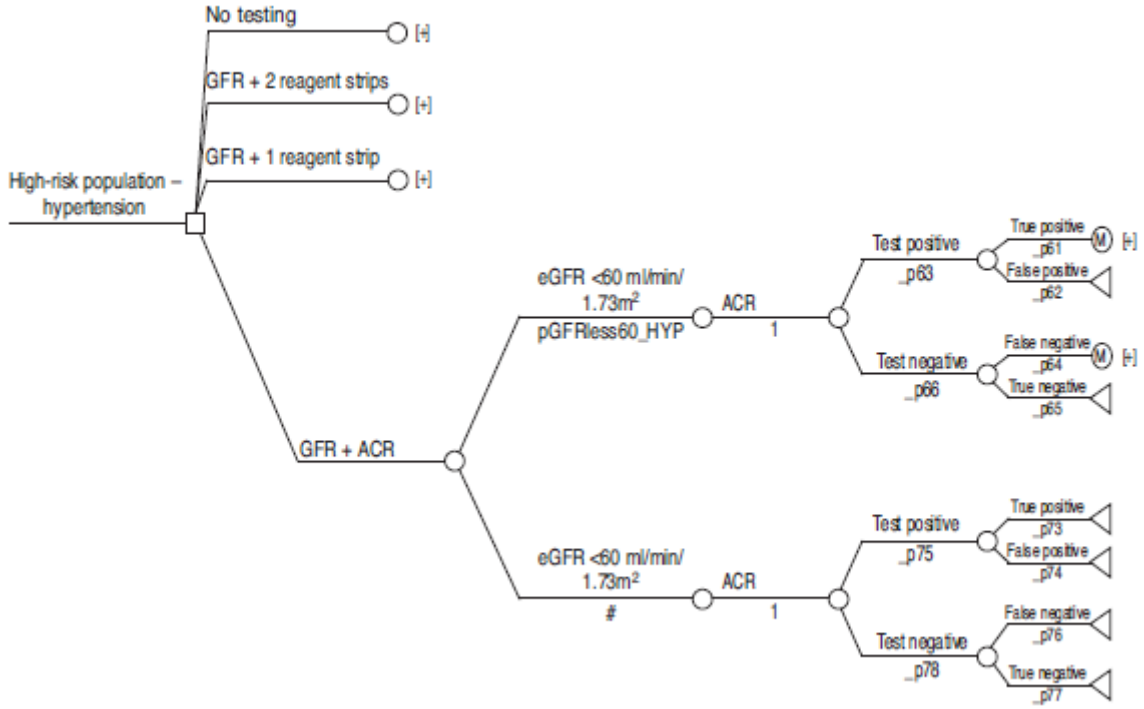
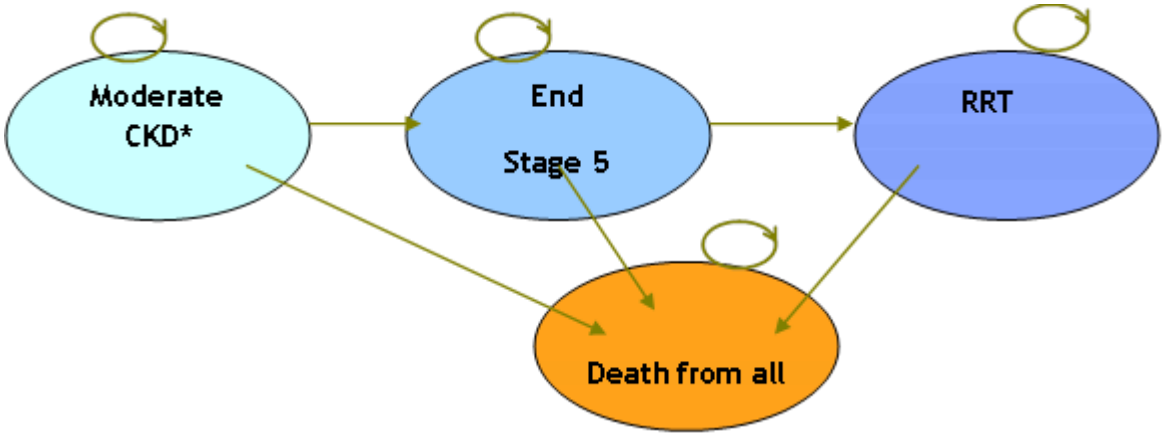


Figure 276: Markov model for patients diagnosed with CKD and proteinuria.



* Health state at time of diagnosis.

Assumptions used in the model's base case analysis

- For the purposes of the model, the GFR estimation was assumed to be 100% sensitive and specific. The 100% specificity is based on the assumption that false positives will be eliminated because we recommend that a positive test is followed by a second eGFR.
- In the base case analysis, the ACR was assumed to be 100% sensitive and specific. The 100% specificity is based on an assumption that false positives will be eliminated by a second measurement to quantify albuminuria / proteinuria. Alternative values for the sensitivity of ACR were tested by sensitivity analysis.
- Health gain was based on the prescription of high dose ACE inhibitor / ARB therapy on diagnosis of CKD. These drugs reduce mortality and slow down the progression of disease.
- Health gain and long-term costs were estimated only for those patients who have both CKD (eGFR <60) and proteinuria. This was a simplification made to speed up the development of the model, but the model should still capture most of the costs and health benefits as long as eGFR and ACR are relatively specific.
- In the absence of diagnosis of CKD (unscreened, false negatives, and true negatives), patients are not prescribed ACE inhibitor / ARB therapy. They receive no CKD treatment until renal replacement therapy (in the discussion below, we consider the impact of relaxing this assumption).

The decision model sought to capture the following effects:

- Health effects
  - Health gain is based on the prescription of high dose ACE inhibitor / ARB therapy on diagnosis of CKD. These are known to reduce mortality and slow down the progression of disease.
  - Some of the screened patients have increased length of life due to ACE inhibitor / ARB therapy
  - Quality of life will be improved by ACE inhibitor / ARB therapy slowing the progression of disease
  - With the ACR strategy, the gains will be greater than reagent strip strategy, since ACR is more sensitive and will detect more eligible cases
- Cost effects
  - Testing strategies will increase spending in the short-term (including staff time, test costs & drug costs). A range of cost estimates obtained from NHS laboratories was used in a two-way sensitivity analysis.
  - In the longer term, some costs will be reduced because ACE inhibitor / ARB therapy slows progression of disease
  - Also, in the longer term, some costs will be increased because patients survive for longer with ACE inhibitor / ARB therapy

Q.3.2.4 Data Sources

Disease prevalence

The prevalence of renal insufficiency (GFR estimated from serum creatinine) and proteinuria/macroalbuminuria (from a random ACR) was determined in different age categories in various adult screening groups in the cross-sectional NHANES III study..[220,222] A total of 14,622 adults that represented the American non-institutionalised population were included in this study.

Table 219: NHANES III[220,222] prevalence of CKD stages 3-5 (GFR <60 ml/min/1.73m^2) by age.

Age	People who do not have diabetes but do have hypertension	People who neither have diabetes nor hypertension
20-39	4.4%	2.1%
40-59	6.7%	4.3%
60-79	19.6%	9.1%
80+	31.5%	21.5%

Table 220: NHANES III[220,222] prevalence of macroalbuminuria (ACR >38 mg/mmol) by age.

	People who do not have diabetes but do have hypertension		People who neither have diabetes nor hypertension	
Age	GFR< 60 ml/min/1.73m^2	GFR ≥60	GFR<60	GFR ≥60
20-39	12.8%	0.5%	0.4%	0.2%
40-59	7.0%	1.3%	0.1%	0.2%
60-79	4.7%	1.0%	0.2%	0.9%
80+	6.7%	3.8%	3.0%	0. 1%

The prevalence of 'cases', those that will be treated with high dose ACEI/ARB therapy after diagnosis, is calculated as the prevalence of GFR <60 ml/min/1.73m^2 multiplied by the prevalence of macroalbuminuria. So for example:

- In people with hypertension aged 60, the prevalence of cases is 19.6% x 4.7% = 0.921%
- In people who do not have hypertension, aged 60, the prevalence of cases is 9.1% x 0.2% = 0.018%

Diagnostic accuracy

Estimates regarding the sensitivity and specificity of the reagent strip test and ACR were decided upon following consideration of previous models, the CKD guideline reviews of clinical evidence and GDG member expert opinion.

For the purposes of the model, the GFR estimation is assumed to be 100% sensitive and specific. The sensitivity and specificity of ACR was also assumed to be 100% in the base case analysis. For both GFR and ACR a second test was costed following an initial positive test.

The sensitivity (92%) and specificity (62%) of the reagent strip test were averages from the two studies[523,609] in the clinical review that measured sensitivity and specificity with a cut-off of 0.3g/l (equivalent to 0.5g/day), the threshold that was identified as most clinically relevant by the GDG.

Effectiveness of ACE inhibitor / ARB therapy

A systematic review of ACE inhibitor treatment for non-diabetic nephropathy (mainly people with hypertension) reported a relative risk reduction in progression to end-stage renal disease of 31% (95% CI 6–49%) compared with no ACE inhibitor treatment (N=1860).[307] The review did not contain evidence with regard to the effects on mortality. For this we turned to the Cochrane review on ACE inhibitor treatment in diabetic nephropathy.(N=3215).[657] The relative risk reduction for death was 22% (95% CI 2–39%).

These relative risk reductions were assumed to apply to true positive patients in both models (both with and without hypertension).

It was assumed that a proportion of patients would be put on ARBs because they could not tolerate ACE inhibitors. For this proportion we used 6% (the proportion of patients experiencing cough after ACEI therapy).[657] It was assumed that patients on ARB therapy would experience the same treatment effects as those on ACEI therapy; only drug costs would differ. Mortality associated with adverse events is incorporated in the estimates of overall mortality. Morbidity due to adverse events is difficult to quantify; the trial data does not suggest that there is major morbidity.

Progression to ESRD

To estimate progression to ESRD we followed the method of one of the previously published models,[282,283] using the following data:

- Annual rate of progression in patients with no diabetes, no hypertension and no proteinuria, from the Okinawa screening study[302] with a sample of 2485 and 7 years, 9 months of follow up = 0.004061 = –ln(1–(77/2485))/7.75
- Probability of progression in first 12 months in patients with no diabetes, no hypertension and no proteinuria, calculated from the annual rate above = 0.004053 = 1–exp(–0.004061)
- Relative risk of progression: proteinuria vs.no proteinuria = 3.858 (sourced from the Okinawa screening study[302])
- Relative risk of progression: hypertension vs.normotension in people with proteinuria = 2.08 (sourced from Jafar et al.'s 2003 meta-analysis[308])
- Relative risk of progression: ACE inhibitors vs.no ACE inhibitors = 0.69 (sourced from Jafar et al.'s 2001 meta-analysis[307])

We used the following annual transition probabilities in the model:

- Hypertension and proteinuria - untreated (Z) = b*c*d = 0.033
- Hypertension and proteinuria - treated (Y) = Z*e = 0.022
- Normotension and proteinuria - untreated (X) = b*c = 0.016
- Normotension and proteinuria - treated (W) = X*e = 0.011

For the tested true positive participants, a 31% reduction in progression from stage 3A/3B/4 to stage 5 was assumed. This was based on a relative risk of 0.69 reported by Jafar et al. 2001, a meta-analysis on 1860 non-diabetic patients who were mainly hypertensive.

Progression from ESRD to RRT

We were aware that not everyone with ESRD receives renal replacement therapy and did not want to over-estimate the cost savings in RRT. We tentatively estimated progression from ESRD to RRT as follows:

- •incidence of RRT in England per million population = 104 per million (UK Renal Registry 2006)[36]
- •population of England = 55 million
- •new cases of RRT in England per year = 5720 (= a*b)
- •prevalence of ESRD = 0.07% (Optimal Renal Care UK[718])
- •cases of ESRD in England = 38,500 (= d*b).

We estimate the annual progression probability from ESRD to RRT to be c/e = 5720/38,500 = 0.149

Mortality

Table 221: Hazard ratio for death according to CKD stage and age (O'Hare et al.[498])

Age	CKD stage 3A/3B/4	CKD stage 5
18 - 44	2.14	5.86
45 - 54	1.83	4.47
55 - 64	1.64	4.29
65 - 74	1.32	3.82
75 - 84	1.22	3.68
85+	1.14	3.6

All-cause mortality rates were calculated using the hazard ratio for death for CKD patients stratified by age and GFR.[498] To get the age-specific death rates for the model, these ratios were multiplied with the age-specific death rates for the general population in England and Wales.[235]

For the true positives, the mortality rate was reduced by 22%, attributable to ACE inhibitor / ARB therapy.

Costs

Direct costs of medical care related to CKD and hypertension were included. All costs were in 2006–7 UK pounds sterling. The costs of testing incorporated initial GFR estimation, reagent strip testing and/or ACR estimation and GP practice nurse time costs (see Table 222).

It was assumed that following a GFR test result, high-risk individuals would be requested to visit the GP surgery to provide a urine sample for urinalysis. They may be attended to by either the practice nurse or health care assistant. Therefore a single visit to a GP practice nurse is accounted for in testing strategies 3 and 4. In strategy 2, a second visit is costed if the first urinalysis is negative.

Following the review and recording of results, action may involve no further assessment or may contribute to a follow-up appointment with GP or practice nurse or a referral to specialist care.

Table 222: Base case unit costs.[145,162]

Unit costs		Reference
Haematology	£ 2.78	NHS Reference Costs, 2006
Biochemistry	£ 2.03	NHS Reference Costs, 2006
ACR (Albumin-to-Creatinine Ratio)	£ 3.10 *	Brighton Laboratory
Phlebotomy	£ 2.96	NHS Reference Costs, 2006
Bayer 10SG Multistix Reagent Strip Tests	£ 0.21/ strip	Reference cost for Kent and Medway
PTH assay	£15.00	Reference cost for Kent and Medway
25-hydroxy Vitamin D assay	£15.00	Reference cost for Kent and Medway
GP Care - Per surgery consultation lasting 10.0 minutes	£25.00	PSSRU 2006
Nurse (GP Practice) per consultation/procedure	£8.00	PSSRU 2006
Ultrasound	£75.14	NHS Reference Costs, 2006
Nephrology Outpatient : First attendance	£242.47	NHS Reference Costs, 2006
Nephrology Outpatient: Follow up attendance	£135.84	NHS Reference Costs, 2006

** Alternative values were tested in a two-way sensitivity analysis, discussed below.*

Drug costs

Costs of antihypertensive drug therapy were based on prices quoted in the British National Formulary.[6] The baseline drug regimen adopted for hypertensive patients was a calcium channel blocker and thiazide diuretic. These drugs are the most widely prescribed for hypertension.[211]

Table 223: Drug costs - Hypertension with untreated CKD.

Drug	Dose/schedule	Proportion of patients (a)	unit cost per 28 tab pack (b)	Cost/year (c = 13.04*b)	Weighted average cost per patient per year (d = a*c)
Bendroflumethiazide	2.5 mg od	100 %	£1.43	£18.64	£18.64
Amlodipine	10 mg qd	100 %	£3.08	£40.15	£40.15
Total drug cost of hypertension and CKD treatment					£58.79

The costs of full-dose ACE inhibitor / ARB therapy for CKD treatment in people with hypertension and people with neither diabetes nor hypertension are represented in Table 224and Table 225. The drug costs are different for those with neither diabetes nor hypertension, inasmuch as there are no drug costs for hypertension other than ACE inhibitor / ARB therapy for the true positives.

Table 224: Drug costs – hypertension with treated CKD.

DRUG	dose/schedule	proportion of patients (a)	unit cost per 28 tab pack (b)	Cost/year (c = 13.04*b)	Weighted average cost per patient per year (d = a*c)
Bendroflumethiazide	2.5 mg od	100 %	£1.43	£18.64	£18.64
Amlodipine	10 mg qd	100 %	£3.08	£40.15	£40.15
Ramipril	10mg	94 % *	£3.16	£41.19	£38.72
Irbesartan	300mg od	6 % *	£16.91	£220.43	£13.23
Total drug cost of hypertension and CKD treatment					£110.74

**0.06 based on Strippoli et al.*

Table 225: Drug costs – no hypertension, no diabetes, treated CKD.

DRUG	dose/schedule	proportion of patients (a)	unit cost per 28 tab pack (b)	Cost/year (c=13.04 X b)	Weighted average cost per patient per year (d=a x c)
Ramipril	10mg	94 % *	£3.16	£41.19	£38.72
Irbesartan	300mg od	6 % *	£16.91	£220.43	£13.23
Total drug cost of hypertension and CKD treatment					£51.95

**0.06 based on Strippoli et al. 2006 – see text.*

GP care costs

The number of visits per year was determined by whether they or not they are diagnosed with hypertension or CKD (Table 226). People were assumed to have pathology tests at £7.78 per year[162] regardless of whether or not they are diagnosed with hypertension.

Table 226: General practitioner care costs.

	GP visits per patient per year*	GP visit costs (£) per patient per year
Non-diabetic, hypertensive - treated	6	£150
Non-diabetic, hypertensive - un treated	4	£100
Non-diabetic, non- hypertensive - treated	4	£100
Non-diabetic, non-hypertensive - untreated	2	£50

** The number of GP visits per year made by people with hypertension and CKD, was sourced from the Australian CKD model.[282,283] For the people without hypertension, the number of visits was assumed.*

*** The cost of a GP visit was £25.[145,146]*

Specialist nephrology outpatient care costs

Using the NEOERICA database, Klebe et al.[346] estimated the outpatient nephrology service use and costs for people with CKD stage 3–5 not receiving renal replacement therapy, assuming that the guidelines of the Royal College of Physicians and Renal Association are followed.[346] This analysis of a UK database identified the proportion of patients within each CKD stage that would require nephrology referral, nephrology follow up and further investigations in the form of ultrasound scans and blood tests for anaemia, parathyroid hormone concentration, vitamin D estimation etc. The use of services was divided according to resources required on diagnosis of CKD as well as the annual use after diagnosis. The numbers of visits per year, by CKD stage[346] were multiplied by the NHS reference cost for a nephrology outpatient visit.[162] Pathology tests were taken from the costing study.[346] The costs for CKD stage 3–4 was weighted according to the prevalence of CKD stage 3 and 4.[220,222]

Table 227: Specialist nephrology outpatient care costs according to CKD stage.

	CKD stage 3-4	CKD stage 5
On diagnosis (referral costs + diagnostic tests : lab + ultrasound)	£ 185.52	£ 756.23
Annual costs (follow up + lab tests)	£ 415.41	£ 438.63

Cost of inpatient care

Table 228: Cost of hospitalisation according to age and CKD stage – any cause.[162,505,672]

	Relative risk of admission (compared with the general population)			
CKD stage 3–4	1.8			
CKD stage 5	3.1			
	Mean admissions per year			
	Age15–44	Age 45–64	Age 65–74	Age 75+
General Population	0.20	0.24	0.45	0.75
CKD stage 3–4	0.36	0.44	0.83	1.35
CKD stage 5	0.63	0.75	1.42	2.33
	Cost per year			
	Age15–44	Age 45–64	Age 65–74	Age 75+
CKD stage 3–4	£340	£408	£1339	£2193
CKD stage 5	£587	£703	£2306	£3776

A general hospital admission rate was calculated for England and Wales, and combined with the hazard ratio for any hospital admission according to CKD stage (from Go et al.[229,230]) produced an admission rate by CKD stage. Using reference costs for general renal disorder admissions that were differentiated by age, the cost of inpatient admissions according to age and stage were calculated.

Cost of renal replacement therapy

According to the 2006 UK Renal Registry Report,[36] haemodialysis was the first modality of RRT in 76% of patients, peritoneal dialysis in 21% and transplant in 3%. The cost of RRT was weighted according to these proportions.

The cost of a renal transplant used in the model was £20,000 in the first year and £6500 per year for the years following transplantation (Palmer et al.[518,690]). These costs include hospitalisation, drugs and treatment of complications.

Table 229: cost of dialysis.[36,47]

	Haemodialysis HD (main unit)	Haemodialysis HD (satellite unit)	Automated Peritoneal Dialysis (APD)	Continuous perambulatory Peritoneal Dialysis (CPD)
	Cost £	Cost £	Cost £	Cost £
Direct nursing	7969	7071	371	357
other nursing activities	2132	1905	1995	1995
disposables	10,952	10,952	14,152	9772
medical supervision	1117	1026	901	901
dialysis machines	720	720	924	-
machine maintenance	766	583	766	-
anaemia therapy	3740	3328	2140	2140
hospital transport	2438	1905	114	114
overheads	5188	5179	290	290
Total cost	35,022	32,669	21,655	15,570
Total cost on HD/PD	33,845		18,613	
Proportion on HD/PD	76%		21%	

Utilities

A Utility score of 0.734 was used for CKD stages 3 and 4. It was sourced from the Australian model.[282,283] This score captures the utility for hypertensive patients on therapy. The Australian model used utility-based quality of life scores derived from data collected in the Australian Diabetes and Lifestyle study (Ausdiab).[110,111] A cross-sectional study of 11,246 non-institutionalised Australians aged 25 years or older.

A Utility score of 0.603 was used for patients in CKD stage 5 and on RRT (de Wit et al.[154,158]). This study assessed the health-related quality of life (HRQOL) of 135 haemodialysis and peritoneal dialysis patients.

Q.3.3 Results for model 1: hypertension but no diabetes

Q.3.3.1 Base case analysis

The base case consisted of opportunistic case finding in women with hypertension aged 60 years who present to primary care with a GFR <60 ml/min/1.73m^2 and previously undetected proteinuria. The number of years in each stage of CKD, on RRT and QALYs resulting from each strategy is presented in Table 230. The ACR strategy picks up the most number of cases and has the highest QALYs. The 'reagent 1 strategy' finds the least amount of cases compared to the 'reagent 2 strategy' and the 'ACR strategy'.

Table 230: Base case results (women aged 60 with hypertension but not diabetes): health outcomes per case.

	No testing	Reagent 1	Reagent 2	ACR
Mean years in CKD Stage 3-4	15.44	18.22	18.44	18.46
Mean years in CKD Stage 5 (no RRT)	2.14	1.83	1.81	1.81
Mean years in CKD Stage 5 (RRT)	2.01	1.63	1.60	1.60
Mean life years	19.59	21.68	21.85	21.86
Cases found (as a proportion of the tested population)	0%	0.848%	0.915%	0.921%

The costs of testing were highest in the 'reagent 2 strategy' as were overall costs. The costs of RRT were highest in the no testing strategy.

For the hypertensive population, the base case analysis, the key result is that testing is cost-effective for all ages and that ACR after GFR is the most cost-effective strategy (Table 231 and Table 232). The incremental cost-effectiveness thresholds were below £20,000 per QALY gained. The 'ACR strategy' dominates the 'reagent 2 strategy': that is, the ACR strategy is cheaper and more effective.

Table 231: Model 1 base case results (women aged 60 with hypertension but not diabetes).

Strategy	Cost	Effectiveness	Increment C/E (ICER)
With all options			
No testing	£506.7	0.0923 QALY	
Reagent 1	£516.7	0.0996 QALY	1,362/QALY
ACR	£517.8	0.1005 QALY	1,327/QALY
Reagent 2	£521.9	0.1004 QALY	(Dominated)
Without dominated options (simple or extended)			
No testing	£506.7	0.0923 QALY	
ACR	£517.8	0.1005 QALY	1,358/QALYs

Table 232: Model 1 base case results: cost-effectiveness by age and sex.

	Men	Women
Age 20	The 'ACR strategy' dominates the 'no testing strategy'	The 'ACR strategy' dominates the 'no testing strategy'
Age 40	The 'ACR strategy' dominates the 'no testing strategy'	The 'ACR strategy' dominates the 'no testing strategy'
Age 60	The 'ACR strategy' is cost-effective	The 'ACR strategy' is cost-effective
Age 80	The 'ACR strategy' is cost-effective	The 'ACR strategy' is cost-effective

**cost-effectiveness threshold=£20,000 per QALY gained*

Q.3.3.2 One-way sensitivity analysis (women aged 60 with hypertension)

There were no important differences in the results of the sensitivity analysis for men and women. Therefore the results of the base case are reported. We conducted threshold analyses to see how extreme a value a parameter would have to take before the optimal strategy switched.

Prevalence and test accuracy

The prevalence of GFR <60 ml/min/1.73m^2 was varied between 0 and 100%. At a prevalence as low as 1.4%, the 'ACR strategy' remained cost-effective with an ICER of £30,000 per additional QALY gained.

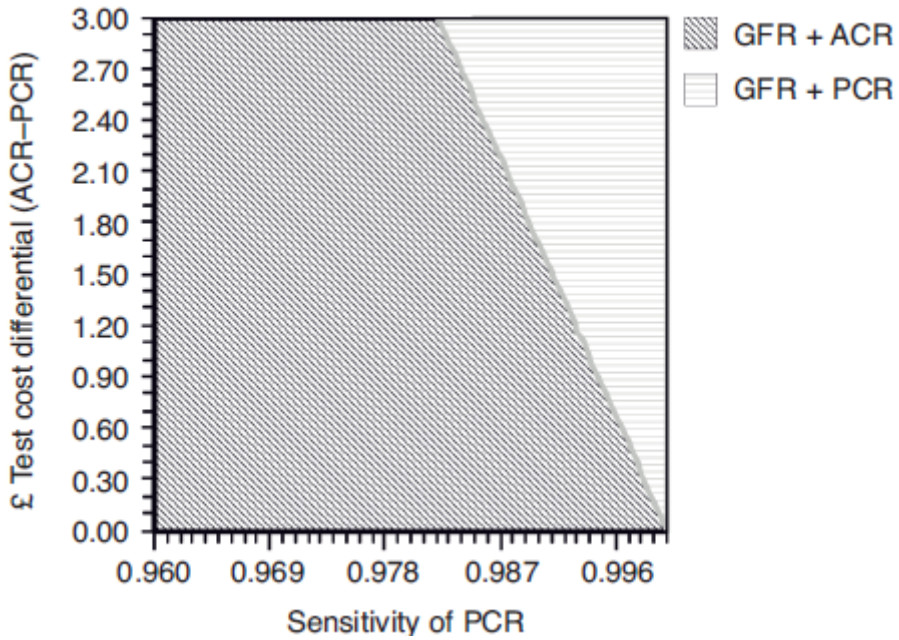
At a prevalence of proteinuria as low as 0.4 % the 'ACR strategy' had an ICER of £24,000 per additional QALY gained.

The sensitivity of ACR testing was varied between 0 and 100%. Only if the sensitivity is below 11% is the 'ACR strategy' not cost-effective compared with no testing.

Q.3.3.3 Two-way sensitivity analysis (ACR vs.PCR)

A 5th strategy ('PCR strategy') was added to the model. This strategy involved a combination of testing eGFR and then PCR. The reagent costs of PCR were assumed to be cheaper than that of the ACR by 40p per test. When PCR was assumed to be both as sensitive and as specific as ACR, the 'PCR strategy' proved to be most cost-effective. The 'PCR strategy' dominated the 'ACR strategy'. However, at PCR sensitivities less than 99.8%, the 'ACR strategy' is more cost effective (assuming as before that ACR is 100% sensitive and specific). Figure 277 shows when the 'ACR strategy' becomes cost-effective given different levels of PCR sensitivity and differential cost. The greater the difference in price between ACR and PCR, the lower the sensitivity of PCR has to be for the 'ACR strategy' to still be cost-effective.

Figure 277: Two way sensitivity analysis (ACR vs. PCR)



NB: Sensitivity of ACR=100%
No testing, GFR + 2 reagent strips, GFR + 1 reagent strip do not appear in the graph as they were not cost-effective

Q.3.3.4 Other sensitivity analyses

Progression rates

Even at a 0.01% rate of progression to ESRD, the 'ACR strategy''s ICER was still only £12,000/QALY compared to the 'no testing strategy'.

If we assume that every patient who progresses to ESRD is automatically placed on RRT, the ACR strategy still proves.

Effectiveness of treatment

When the treatment effect of ACE inhibitor / ARB therapy on progression is varied while keeping the treatment effect on mortality constant (RR=0.78), the results are insensitive. Even with no effect of ACE inhibitor / ARB therapy on progression, the 'ACR strategy' is marginally cost-effective at £22,000 per QALY gained.

If we assume no treatment effect on mortality (applying a mortality rate of an untreated CKD population), then if the relative risk reduction on progression is decreased below 11%, the 'ACR strategy' ceases to be cost-effective.

When the treatment effect on mortality is varied between 0 and 100% reduction, while keeping the treatment effect on progression to ESRD constant (RR= 0.69) the 'ACR strategy' is most cost-effective throughout.

Cost of RRT

The annual cost of renal replacement therapy was varied between £5000 and £100,000. At an annual cost as low as £5000 for RRT, the 'ACR strategy' remained cost effective at £9000 per additional QALY gained. At the other extreme, at an annual cost of £100,000 the 'ACR strategy' dominated the other strategies.

Cost of drugs

If all patients with CKD were placed on the more expensive drug (high dose ARB instead of high dose ACE inhibitor), the 'ACR strategy' is still the most cost effective with an ICER of £4,000 per QALY gained.

Nurse practitioner time costs

The cost per consultation was varied between £0 and £25 (equivalent to the cost of an 8 minute GP consultation). Even if the testing time costs were free, the 'ACR strategy' remains the most cost-effective at £9000 per additional QALY compared with the 'reagent 2 strategy'.

Specialist outpatient care

The effect of the costs of specialist care were explored by setting the costs at high and low estimates, using the interquartile range from the NHS reference costs. At the high estimate, the 'ACR strategy' was still the most cost effective.

RRT mortality

The mortality rate while on RRT was also explored. The model proved to be insensitive to changes in this rate. At a mortality hazard ratio of 5 the 'ACR strategy' has an ICER of £6000/QALY.

Q.3.4 Results for model 2: neither diabetes nor hypertension

Q.3.4.1 Base case analysis

Of the four strategies, the 'ACR strategy' detected the most cases (GFR <60 ml/min/1.73m^2 and macro-albuminuria) and yielded the most QALYs (Table 234) – this is not surprising since the ACR test was assumed to be 100% sensitive and specific. The testing strategies yielded some cost savings in terms of reduced renal replacement therapy. But, due to the low prevalence of cases in the population, these savings were small compared with the costs of testing. The most costly strategy was 'reagent 2' followed by 'ACR', 'reagent 1' and least costly was 'no testing'. None of the testing strategies were cost-effective compared with not testing for the base case (55-year old women): all three testing strategies cost more than £400 000 per QALY gained (Table 234). Indeed testing wasn't cost-effective for any age group except age 80 where the prevalence was highest and reduction in mortality greatest (Table 235).

Table 233: Base case results (women aged 55 with neither diabetes nor hypertension): health outcomes per patient tested.

	Mean			
	No testing	Reagent 1	Reagent 2	ACR
Years in CKD stage 3-4	21.41	24.25	24.48	24.50
Years in CKD stage 5 (no RRT)	1.50	1.24	1.22	1.22
Years in CKD stage 5 (RRT)	1.69	1.33	1.30	1.29
Life-years	24.60	26.82	27.00	27.01
Cases found	0.0000%	0.0040%	0.0043%	0.0043%

Table 234: Model 2 base case results: cost per QALY gained

Strategy	Cost	Effectiveness	Incremental C/E (ICER)
All strategies			
No testing strategy	£1.9	0.00050 QALY	
Reagent 1 strategy	£16.9	0.00053 QALY	489,899 /QALY
ACR strategy	£18.3	0.00054 QALY	411,726 /QALY
Reagent 2 strategy	£21.8	0.00054 QALY	(Dominated)
Without dominated options (simple or extended)			
No testing strategy	£1.9	0.00050 QALY	
ACR strategy	£18.3	0.00054 QALY	482,082 /QALY

Table 235: Model 2 base case results: cost-effective strategy by age and sex.

	Males	Females
Age 20	No testing was cost-effective	No testing was cost-effective

	Males	Females
Age 40	No testing was cost-effective	No testing was cost-effective
Age 55	No testing was cost-effective	No testing was cost-effective
Age 65	No testing was cost-effective	No testing was cost-effective
Age 70	No testing was cost-effective	No testing was cost-effective
Age 75	No testing was cost-effective	No testing was cost-effective
Age 80	ACR was Cost-effective at £11,000 /QALY compared with no testing	ACR was Cost-effective at £11,000 /QALY compared with no testing

**cost-effectiveness threshold=£20,000 per QALY gained*

Q.3.4.2 One-way sensitivity analysis

It is only at a 96% prevalence of GFR <60 ml/min/1,73m^2 that the 'ACR strategy' becomes cost-effective for both males and females aged 55.

One-way sensitivity analysis revealed that only if the prevalence of proteinuria was increased two-fold to 3%, would the 'ACR strategy' be cost-effective for females aged 55.

The 'ACR strategy' was not cost-effective even if ACE inhibitor / ARB therapy was 100% effective in preventing mortality or progression to ESRD.

Q.3.5 Discussion

Q.3.5.1 Summary

People with hypertension and no diabetes

The base case analysis indicates that testing adults of various ages with hypertension with a single ACR test is highly cost-effective. The initial use of ACR is more cost-effective than ACR after a positive reagent strip test. The results were not sensitive to changes in any individual model parameter.

The results are not sensitive to the individual treatment effect of ACE inhibitor / ARB therapy on progression or the effect of ACE inhibitor / ARB therapy on mortality. But when both parameters were covaried, testing and consequent treatment was not always cost-effective.

The model shows that ACR is more cost-effective than PCR if it is more sensitive than the PCR test at selecting appropriate patients for ACE inhibitor / ARB treatment (by more than 0.2% sensitivity if the cost differential is purely comprised of reagent cost differences). There is no clinical evidence to support or refute this, since ACR and PCR have not been compared to the same appropriate reference standard. However the GDG concluded that the required difference in sensitivity was small and plausible given biochemical reasons to suggest that albuminuria is more useful in predicting progression (these are discussed in sections 4.3 and 4.4 of the full guideline).

People with no hypertension and no diabetes

Base case analysis indicates that testing of non-hypertensive, non-diabetic adults at ages 55–79 is not cost-effective. At age 80, testing appeared to be cost-effective.

Q.3.5.2 Limitations

Limitations that potentially bias in favour of testing

Reduction in all-cause mortality due to treatment with high dose ACE inhibitor / ARB therapy is not proven (except for diabetic populations), although the evidence is suggestive of a treatment effect.

The model assumes that without testing, patients who progress rapidly are not detected until they require RRT. Clearly some patients will be picked up before RRT due to incidental testing but we believe this number would be small compared to the number of 'crash landers' that are diagnosed at the RRT stage.

Compliance with medication might be less than observed in trials and therefore effectiveness might be over-estimated but this is difficult to quantify.

In the base case analysis, ACR is assumed to be 100% sensitive and 100% specific. The results were not sensitive to the sensitivity of ACR. However, even in the sensitivity analysis, the model does not measure the health impact or long-term costs of false positives. We believe these to be very small effects as a consequence of repeat testing after a positive test result.

In the base case analysis we include the costs and health effects of ACE inhibitor / ARB treatment for all patients. We acknowledge that a large proportion of patients may be on low dose ACE inhibitor. The cost-effectiveness for this group is difficult to quantify but may not be very different from other patients. This is because, although such patients are likely to get less health gain from treatment they are also likely to incur less incremental cost.

Limitations that potentially bias in favour of no testing

Benefits of early diagnosis other than from ACE inhibitor / ARB therapy are not captured. We assume that patients diagnosed at stage 3 or 4 receive specialist nephrological care, yet the benefits of this care are not included.

A number of questions were not addressed by the model

The model essentially evaluates testing at one time point only. It does not evaluate repeat testing of negatives or monitoring of positives.

The model does not evaluate testing for CKD risk factors, such as testing for hypertension.

The model does not evaluate testing of high-risk groups other than people with hypertension, such as long-term users of potentially nephrotoxic drugs, for whom the incidence of CKD is not known.

Q.3.6 Conclusions

The model suggests that case-finding among high-risk groups is cost-effective. Use of albumin:creatinine ratio, without prior reagent strip, appears to be the most cost-effective option

Q.4 Appendix D: GDG members' declarations of interest

Name	Personal pecuniary interest	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
BAKHSHI Lina	None	None	None	None
BENETT Ivan	42 GlaxoSmithKline shares	None	None	None
CROWE Emily	None	None	None	None
DODWELL Miranda	None	None	None	None
DUNN Robert	None	None	- National Advocacy Officer - National Kidney Federation	None
FORREST Caroline	None	None	None	None
GOLDBERG Lawrence	None	None	None	None
HALPIN David	Received fees for lectures and sitting on advisory boards and have received travel expenses and accommodation to attend scientific meetings from GlaxoSmithKline (GSK), Astra Zeneca, Boehringer Ingelheim, Pfizer and Altanapharma	None	My department has undertaken commercial research trials for GSK, Astra Zeneca, Boehringer Ingelheim, SR Pharma, Almirall and Novartis	None
HARRIS Kevin	- Member of Baxter Medical Advisory Board 2006/7 (non-specific) - Member of Genzyme Medical Advisory Board 2006/7 (non-specific) - Member of Shire Medical Advisory Board 2006 (non-specific) - Member of Novartis Medical Advisory Board 2006 (non-specific) - Lecture for BMS/Sanofi, Pfizer, GSK, Boehringer Ingelheim on CKD (non-specific)	None	- Departmental funding for bone management nurse (Genzyme) - Unrestricted educational grant from Fresenuis - Support for clinical fellowship from Baxter - Support for part time clerical post from Amgen - Departmental reimbursement for my time to be a	- Current chair for the Clinical Services Committee of the Renal Association - Clinical Vice President Elect of the Renal Association

Name	Personal pecuniary interest	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
			member of the Optimal CKD Management Programme Board (ended September 2006)	
JOHN Ian	None	None	None	None
LAMB Edmund	None	None	None	None
MCINTRYE Natasha	- Evening workshop for Pfizer on GPs and CKD management - Evening workshop for Bristol Myers Squibbs (BMS) on primary care and CKD management Global nurse advisory board for Hoffman Roche - Masterclass for Roche Working as a consultant on a six month project for Riche but not as an employee	None	None	None
OMARJEE Suffiya	None	A family member conducts drug trial research for several drug companies in the field of gastroenterology in South Africa.	None	None
O'RIORDAN Shelagh	None	None	None	None
RODERICK Paul	Advisor to GlaxoSmithKline regarding drug nephrotoxicity	None	Grant funding from Pfizer for a research fellow	None
STEPHENS David	None	None	None	None
STEVENS Paul	Honoraria for lectures and attendance at	None	Roche UK research grant for	None

Name	Personal pecuniary interest	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
	international meetings for Ortho Biotech, Bayer, Amgen, Pfizer and Hoffman La Roche		developing an expert system for the management of chronic kidney disease	
SUTTON Jaim	None	None	None	None
TOK Meiyin	None	None	None	None

Q.5 Clinical evidence tables from 2008 guideline

Q.5.1 Factors affecting the biological and analytical variability of GFR estimated from measurement of serum creatinine (2014 guideline – chapter 5.2)

Table 236: Ref ID: 4124 [Ford et al. 2008]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ford L, Berg J. Delay in separating blood samples affects creatinine measurement using the Roche kinetic Jaffe method. 2008.	Case series Evidence level: 3 1 centre, UK	N volunteers = 10 N outpatients = 113	**Inclusion:** volunteers and outpatients **Exclusion:** not stated **Population baseline characteristics:** Volunteers (N=10) age 27-55 years; 90% Caucasian, 10% Asian, 50% male Outpatients (N=113): age 18-88 years, 52%	Effect of delay in centrifugation of blood samples on creatinine concentration determined by Kinetic Jaffe reaction (Roche kit). N=10 volunteers N=113 outpatients **Procedure:** Un-separated Blood experiment: 10 volunteers each provided 7 blood samples (clotted). Samples were kept at RT exposed to light until centrifugation at 0.5 h, 4 h, 8 h, 16 h, 24 h, 36, and 48 h-post collection. All samples were assayed for creatinine with the kinetic Jaffe Roche method standardised against IDMS.	Timely centrifugation of blood samples on creatinine concentration N=10 volunteers N=113 outpatients	Not applicable	Change in creatinine concentration with delay in centrifugation of blood sample Change in GFR with delay in centrifugation of blood sample	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Caucasian, 39% Asian, 8% Afro-Caribbean, 44% male	Separated Serum experiment: 10 outpatients each provided a blood sample that was allowed to clot and then centrifuged after 0.5h. The separated (centrifuged) serum was then left at RT exposed to light and aliquots were taken for analysis (kinetic Jaffe, Roche) at 0.5, 4, 8, 16, 24, 36, and 48 h. 24-h Delay Study: Clotted blood samples were collected in duplicate from N=113 outpatients. The first sample was centrifuged at 0.5h, while the second clotted sample was left un-separated for 24-h at RT, then centrifuged and analysed by kinetic Jaffe (Roche). Creatinine Enzymatic methods: 10 duplicate samples from the 24-h study with the largest difference between creatinine concentration for samples separated after 0.5 h and a delay of 24-h were analysed with an enzymatic creatinine assay (VITROS 5)				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

Baseline = 0.5 h delay in centrifugation of clotted blood.

Effect of delayed centrifugation of blood samples on creatinine concentration (determined by kinetic Jaffe, Roche):

Delayed centrifugation of clotted blood samples (N=10 volunteers) resulted in a significant increase in creatinine concentration after 16 h ($p<0.001$). By 48-h, creatinine concentrations had increased above the baseline (centrifugation after 0.5h) by mean 29% (range 21-63%). Mean CV for the seven measures for each volunteer was 11.3% (range 8.1-16.2%)

There was NS change in creatinine concentrations in centrifuged (separated) serum samples left at RT for 0.5, 4, 8, 16, 24, 36, and 48 h. Mean CV for each sample was 4.87% (range 2.38-7.81%)

From the 24-h delay experiment (N=113 outpatients), creatinine concentration significantly increased from baseline (mean 85 micromol/l) to 24-h delay (mean 95 micromol/l, 11% increase, $p<0.0004$) in centrifugation of blood samples. Similar results were seen for males, females, and different ethnicities.

Eff**ect of delayed centrifugation of blood samples on the eGFR (MDRD)**

With a 16 h delay in centrifugation, 4/7 volunteers with baseline Stage 1 CKD had changed to Stage 2. By 36 h delay in centrifugation, 7/7 volunteers had changed from Stage 1 to Stage 2 CKD. Three volunteers with baseline Stage 2 CKD did not fall to Stage 3 regardless of length of delay in centrifugation.

From the 24-h delay experiment (N=113 outpatients), eGFR significantly decreased from baseline (mean eGFR 85 ml/min/1.73m^2) to 24-h delay (mean eGFR 75 ml/min/1.73m^2, 13% decrease, $p<0.0001$) in centrifugation of blood samples. Similar results were seen for males, females, and different ethnicities.

From the 24-h delay experiment (N=113 outpatients), the CKD staging of 32% of the participants changed after a 24-h delay in centrifugation of blood samples. 26% went from Stage 1 CKD to Stage 2 and 6% went from Stage 2 to Stage 3 CKD.

Effect of delayed centrifugation of blood samples on creatinine concentration (determined by Enzymatic method, VITROS):

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
In contrast to the kinetic Jaffe method (N=10 outpatient samples; mean 29.4% increase in creatinine concentration after 24-h delay in centrifugation, range 19.7 – 86.6%), there was little change in creatinine concentration using the enzymatic method (mean decrease 2.7%, range –13.8 to +8.6%)								

Table 237: Ref ID: 3967 [Fraser et al. 1983]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fraser CG, Williams P. Short-term biological variation of plasma analytes in renal disease. Clin Chem. 1983; 29(3):508-510. Ref ID: 3967	Case series Evidence level: 3	N = 9 patients with CKD (3 mild, 3 moderate, 3 severe CKD) 1 centre, Australia	**Inclusion criteria**: sequentially recruited adults with CKD **Exclusion criteria** : none stated **Population baseline characteristics:** Not stated	Biological variability of serum creatinine in adults with CKD N=9 **Procedure:** Blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h after administration of 150 mg oral dose or ranitidine. Samples were promptly centrifuged, aliquoted into 3 separate aliquots and frozen in liquid nitrogen. Serum creatinine concentration determined in an Astra discrete analyser in a single day (calibrated twice). The first aliquot of all samples from a single subject were placed in random order and analysed in a single batch containing quality-control materials (Wellcomtrol Unassayed and Monitrol II.X Control). The Astra was recalibrated and the second aliquot of all samples from a single subject was analysed the same way.	n/a	Not applicable	Biological variation in serum creatinine measurements	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size The CV for serum creatinine for all nine subjects with CKD on all occasions was 61.9% (mean 190.4 micromol/l; SD 117.8 micromol/l). **Biological Variation in serum creatinine concentration** • The average analytical variation was 0.1% of the total variance. • The average intra-individual biological variation of creatinine measurements was 1.1% of the total variance. • The average inter-individual variation for serum creatinine was 98.8% of the total variance.								

Table 238: Ref ID: 3971 [Holzel et al. 1987]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Holzel WG. Intra-individual variation of some analytes in serum of patients with chronic renal failure. Clin Chem. 1987; 33(5):670-673. Ref ID: 3971	Case series Evidence level: 3	N = 24 healthy volunteers N=17 patients with CKD 1 centre, Germany	**Inclusion criteria:** sequentially recruited healthy adults or adults with CKD. **Exclusion criteria :** none stated **Population baseline characteristics:** Healthy adults: Age range 20-50 years, mean age 33.5 years (female) and 41.8 years (male), CKD group: 65% glomerulonephritis, 29% chronic pyelonephritis, 6% gouty CKD; serum creatinine range: 255-1125 micromol/l.	Biological variability of serum creatinine in adults with CKD N=17 **Procedure:** Blood samples were taken from healthy subjects once a week for 8 weeks. Blood was taken from CKD patients 8 times during 3 weeks and at 4, 8, and 12 weeks after the first collection. Blood samples were drawn after an o/n fast from resting subjects, and samples were centrifuged within 1 hour, and the serum was aliquoted and frozen. Serum creatinine concentration determined with Jaffe method on a continuous flow analyzer. Samples were analysed in duplicate within a single run, in random order. Every tenth sample was a control sample.	Biological variability of serum creatinine in healthy adults N=24	Not applicable	Biological variation in creatinine measurements	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Analyses of blood samples for people with CKD were restricted to blood samples taken within first 3 weeks as CKD process was stable at that time.				
Effect size Within-run analytical coefficient of variation for creatinine was 3.3% (in a concentration range of 40-110 micromol/l). **Biological Variation in creatinine concentration** The intra-individual biological variation of creatinine measurements was significantly higher in people with CKD (N=17, CV=5.3%) than in healthy subjects (N=24, CV=2.7%, p<0.01). The ratios of CV for CKD to healthy patients was 1.93 (p<0.01).								

Table 239: Ref ID: 3970 [Holzel et al. 1987]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Holzel WG. Intra-individual variation of some analytes in serum of patients with insulin-dependent diabetes mellitus. Clin Chem. 1987; 33(1):57-61. Ref ID: 3970	Case series Evidence level: 3	N = 24 healthy volunteers N=27 patients with insulin-dependent diabetes 1 centre, Germany	**Inclusion criteria:** sequentially recruited healthy adults or adults with insulin-dependent diabetes **Exclusion criteria** : none stated **Population baseline characteristics:** Healthy adults: Age range 20-50 years, mean age 33.5 years (female) and 41.8 years (male), IDDM group: Age range 18-52 years, mean age 31.8 years (females) and 38.7 years (males)	Biological variability of serum creatinine in adults with IDDM N=27 **Procedure:** Blood samples were taken from subjects once a week for 8 weeks after an o/n fast from resting subjects, and samples were centrifuged within 1 hour, and the serum was aliquoted and frozen in liquid nitrogen. Serum creatinine concentration determined with Jaffe method on a continuous flow analyzer. Samples were analysed in duplicate within a single run, in random order. Every tenth sample was a control sample.	Biological variability of serum creatinine in healthy adults N=24	Not applicable	Biological variation in creatinine measurements	Not stated

Effect size

Within-run analytical coefficient of variation for creatinine was 3.3% (in a concentration range of 40-110 micromol/l).

Biological Variation in creatinine concentration

The intra-individual biological variation of creatinine measurements was significantly higher in women with insulin-dependent diabetes (N=11, CV=6.53%) than in

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
healthy women (N=14, CV=2.81%, p<0.01). The ratios of CV for IDDM to healthy women was 2.32 (p<0.01). The intra-individual biological variation of creatinine measurements was significantly higher in men with insulin-dependent diabetes (N=16, CV=5.88%) than in healthy men (N=10, CV=2.64%, p<0.01). The ratios of CV for IDDM to healthy men was 2.23 (p<0.01).								

Table 240: Ref ID: 697 [Jacobsen et al. 1979]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jacobsen FK, Christensen CK, Mogensen CE et al. Postprandial serum creatinine increase in normal subjects after eating cooked meat. Proceedings of the European Dialysis & Transplant Association. 1979; 16:506-12, 1979.:506-512. Ref ID: 697	Case series Evidence level: 3	N = 6 1 centre in Denmark	**Inclusion criteria:** sequentially recruited healthy medical students. **Exclusion criteria** : not stated **Population baseline characteristics**: Not stated	Experiment 1: Meat meal N=6 Experiment 2: Raw beef meal N=6 **Procedure:** Experiment 1: After o/n fasting, participants were given a light, non-meat containing breakfast. Participants had a meat-containing lunch containing 500 g goulash (250-300 g beef) and 5 hours later a non-meat supper. Blood samples were taken before and after breakfast, before lunch, and then every hour after lunch until 10 pm. Several days later Experiment 1 was repeated and all 6 participants were given a non-meat lunch. Experiment 2: Participants were given one of the following meals: 300g raw beef, 300g friend beef, 300g boiled beef ingested with the cooking water, 500g goulash (250-300g beef), 500g	Experiment 1: Non-meat meal N = 6 Experiment 2: Cooked Beef meals N=6	Not applicable	Change in creatinine concentration	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				stew (250-300g pork). Blood samples were taken before ingestion of the meal and 3 hours after the meal. Serum creatinine concentration determined by Jaffe reaction on an autoanalyser. 39 samples also assayed for creatinine concentration with ion exchange method ("true creatinine").				

Effect size

Change in creatinine concentration (kinetic Jaffe method)

Experiment 1: Following a cooked meat goulash lunch (N=6), the mean serum creatinine concentration significantly increased from baseline (86 micromol/L, preprandial) to 175 micromol/L, 3 hours postprandially, p< 0.001). By contrast, following a non-meat lunch, a small increase in serum creatinine was observed 1 hour postprandially, but the serum creatinine concentration was relatively unchanged throughout the time course.

A high correlation between serum creatinine determined by autoanalyser and by ion exchange was observed (N=39 samples).

Experiment 2: Ingestion of a raw beef meal did NS affect serum creatinine levels.

By contrast ingestion of any type of cooked beef meal (fried, boiled, goulash beef, or stew pork) resulted in a significant increase in serum creatinine. For example, ingestion of fried beef resulted in an increase from baseline serum creatinine 84 micromol/L to 110 micromol/L 3 hours postprandially (p<0.01). Ingestion of boiled beef + cooking water resulted in a significant elevation in serum creatinine from 87 micromol/L to 163 micromol/L postprandially (p<0.001).

Note: Authors suggest serum creatinine measured after fasting or to instruct patient to avoid meat meals prior to creatinine measurements.

Table 241: Ref ID: 3920 [Mayersohn et al. 1983]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. British Journal of Clinical Pharmacology. 1983; 15(2):227-230. Ref ID: 3920	Case series Evidence level: 3	N = 6 1 centre, USA	**Inclusion criteria:** sequentially recruited healthy male adults. **Exclusion criteria:** not stated **Population baseline characteristics:** Age range 26-38 years, mean age 31, mean weight 73 kg, weight range 65-82 kg	Meat breakfast N=6 **Procedure:** Day 1: All participants were given a light, non-meat containing breakfast: 3 participants had a breakfast containing high amounts of non-meat protein (62g) and 3 subjects had a breakfast of low non-meat protein (11.5g). Subjects had non-meat protein lunch and dinner. Day 2: Each subject ate a breakfast containing 225g of boiled beef. Lunch and dinner the same as Day 1. Fluids were ad libitum. On days 1 and 2, blood samples were taken before and at several time intervals after breakfast. Serum creatinine concentration determined by HPLC (daily calibration curves determined). Creatinine clearance determined from timed urine collections.	Non-meat breakfast N = 6	Not applicable	Change in creatinine concentration	Not stated

Effect size

Change in creatinine concentration (HPLC method)

Following a cooked meat breakfast (N=6), the mean serum creatinine concentration significantly increased from baseline (52% increase, range 36-65%). By contrast, following either a high or low non-meat protein breakfast (control), serum creatinine remained stable (%coefficient of variation: 2.2 to 4.3%).

CrCl did NS change in response to a cooked meat breakfast.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: Authors suggest serum creatinine measured after fasting or to instruct patient to avoid meat meals prior to creatinine measurements.								

Table 242: Ref ID: 3965 [Pasternack et al. 1971]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pasternack A, Kuhlback B. Diurnal variations of serum and urine creatine and creatinine. Scand J Clin Lab Invest. 1971; 27(1):1-7. Ref ID: 3965	Case series Evidence level: 3	N healthy volunteers = 9 N paralysed volunteers = 4 1 centre in Finland	**Inclusion criteria:** sequentially recruited healthy volunteers or paralysed (for greater than 3 years, breathing with respirators and severe muscular atrophy) **Exclusion criteria :** not stated **Population baseline characteristics:** Age range 22-45 years	non-fasting over 24 hours N=9 **Procedure:** Participants fasted for 10 hours prior to the first blood sample taken. Blood samples and urine collections were taken at 7:00, 13:00, 19:00, and at 7:00 the following morning. Meals (cooked meat, potatos, vegetables, bread) were eaten at 11:00 and 16:00, water and other beverages freely taken throughout. Normal activity was allowed from 8:00 to 22:00. In the control experiment, the same participants (excluding paralysed subjects) fasted for 34 hours and blood and urine samples taken as before. During this time, normal activity and water intake was allowed. Serum creatinine concentration determined using picrate method and Lloyd's reagent (103% recovery). Duplicate creatinine determinations differed by 1.12%.	Fasting over 34 hours N = 9	Not applicable	Change in creatinine concentration	Not stated
Effect size **Change in creatinine concentration**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
In non-fasting healthy subjects (N=9) or in paralysed subjects (N=4), the creatinine concentration increased significantly during the day, peaking at 19:00 ($p<0.001$). The creatinine concentration then decreased after 19:00 to 7:00 the next morning. In fasting subjects (N=9), there was a small but significant decrease in creatinine concentration between 7:00 and 13:00 ($p<0.02$) and there was no increase in serum creatinine during the rest of the time course. Fasting abolished the diurnal variation in creatinine concentration.								

Table 243: Ref ID: 423 [Pinto et al. 1991]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pinto JR, Bending JJ, Dodds RA et al. Effect of low protein diet on the renal response to meat ingestion in diabetic nephropathy. European Journal of Clinical Investigation. 1991; 21(2):175-183. Ref ID: 423	Case series Evidence level: 3	N = 10 1 centre, Guy's Hospital, London, UK	**Inclusion criteria**: proteinuric (protein excretion > 0.5g/24-h persistent for at elast 1 year) insulin-dependent diabetic adults with diabetic retinopathy. None were taking ACE inhibitors. 7 were taking antihypertensive drugs **Exclusion criteria :** cardiac failure, clinical/biochemical sign of non-diabetic nephropathy **Population baseline characteristics:**	Meat meal on low protein diet N=10 **Procedure:** Participants were randomly allocated to a 3-week period on a normal protein diet or a low protein diet (isocaloric with normal protein diet and containing 0.5g/kg body weight per day of protein; half from animal and half from vegetable sources) . At the end of 3 weeks, all patients returned to normal protein diets for 1 week and then switched over to the alternative protein diet for another 3 weeks. Diet assessment from a detailed dietary history and 3-day weighted food record. At the end of each diet period, patients' GFR measured by inulin clearance before and after a protein meal, consisting of 80g animal protein provided as lean cooked beef. Serum creatinine measurements made at baseline, at the end of	Meat meal on normal protein diet N = 10	Not applicable	Change in serum creatinine concentration	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Age range 26-38 years, mean age 31, mean weight 73 kg, weight range 65-82 kg	each diet period, and before and after a meat meal given at the end of each diet period. Serum creatinine determined on multichannel autoanalyser.				

Effect size

Protein intake was 45% lower on low protein diet compared with the normal protein diet (p<0.001).

Change in creatinine concentration

Following a cooked meat meal (N=10), the mean serum creatinine concentration significantly increased from baseline (167 micromol/L) to 180 micromol/L in 2 hours (p<0.001) in people on a normal protein diet.

Following a cooked meat meal (N=10), the mean serum creatinine concentration significantly increased from baseline (152 micromol/L) to 161 micromol/L in 2 hours (p<0.02) in people on a low protein diet.

Table 244: Ref ID: 3921 [Preiss et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Preiss DJ, Godber IM, Lamb EJ et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem. 2007; 44(Pt 1):35-42. Ref ID: 3921	Case series Evidence level: 3	Total N = 32 No. ITT 1 centre in UK	**Inclusion criteria:** sequentially recruited Caucasian volunteers (healthy and outpatients) age > 18 years. **Exclusion criteria :** vegetarianism, any reason for not eating a meat diet, renal dialysis, renal transplantation receipients, **Population baseline characteristics:** Age range 18-86 years, median age 54.5, 47% male	Meat meal N=32 **Procedure:** A preprandial blood sample was taken 4 hours after a light, non-cooked meat containing breakfast. Participants had either a meat-containing meal (normal helping)or a vegetarian meal. Blood samples were taken after (1-2 hours postprandially and 3-4 hours postprandially). 3 determinations of creatinine concentration by kinetic Jaffe (Beckman Coulter LX20) , ID-MS chromatograghy , and enzymatic method (Roche Integra Analyser). eGFR determined from kinetic Jaffe creatinine concentration with IDMS version of MDRD equation. Serum cystatin C concentration was also determined (nephelometric immunoassay).	Vegetarian meal N = 23	Not applicable	Change in eGFR Change in creatinine concentration Change in cystatin C concentration	Not required
Effect size **Change in creatinine concentration (kinetic Jaffe method)**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Following a cooked meat lunch (N=32), the median serum creatinine concentration significantly increased from baseline (preprandial) by 20.5 micromol/L 1-2 hours post prandially (p< 0.0001) and by 18.5 micromol/L 3-4 hours postprandially (p<0.0001). Similar results were seen when serum creatinine was measured by ID-MS, and enzymatic methods.

Maximal postprandial serum creatinine concentrations were reached by 18 people at the 1-2 h time and by 12 people at the 3-4 hour time.

By contrast, following a vegetarian lunch (N=23), there was a NS change in median serum creatinine concentration from baseline (preprandial) to 1-2 hours postprandially or 3-4 hours post prandially. Similar results were seen when serum creatinine was measured enzymatically.

Change in eGFR (determined from kinetic Jaffe serum creatinine concentration and MDRD equation)

Following a cooked meat lunch (N=32), the median eGFR significantly decreased from baseline (preprandial) by 24.5 ml/min/1.73 m^2 1-2 hours postprandially (p< 0.0001) and by 20 ml/min/1.73 m^2 3-4 hours postprandially (p<0.0001).

By contrast, following a vegetarian lunch (N=23), there was a small but significant increase in eGFR from baseline (preprandial) to 1-2 hours postprandially (1.0 ml/min/1.73 m^2, p=0.009) or 3-4 hours postprandially (3.5 ml/min/1.73 m^2, p=0.006).

Following a meat meal, 11 people changed from a pre-prandial eGFR > 59 ml/min/1.73 m^2 to a post prandial eGFR of < 60 ml/min/1.73 m^2. Effectively, erroneously placing them in Stage 3 CKD.

Change in cystatin C concentration

Following a cooked meat lunch (N=32), there was NS change in median serum cystatin C before and after a meat lunch..

Following a vegetarian lunch (N=23), there was NS change in median serum cystatin C concentration from baseline (preprandial) to 3-4 hours post prandially.

Note: did not sample past 4 hours, no quantification of the amount of meat eaten (although a “normal” portion size), did not evaluate all the dietary constituents of the meals. Authors suggest eGFR measured after fasting or to instruct patient to avoid meat meals prior to eGFR measure.

Table 245: 3976 [Rapoport et al. 1968]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rapoport A, Husdan H. Endogenous creatinine clearance and serum creatinine in the clinical assessment of kidney function. Can Med Assoc J. 1968; 99(9):149-156. Ref ID: 3976	Case series Evidence level: 3	N patients admitted for investigation of kidney disease, hypertension or kidney stones = 89 1 centre in Canada	**Inclusion criteria:** patients admitted for investigation of kidney disease, hypertension or kidney stones **Exclusion criteria** :heart failure, hyperglycemia, glycosuria, ketonuria **Population baseline characteristics**: 55% male, Age range 14-58 years	Creatinine concentration following fasting in the morning N=72 **Procedure:** Blood specimens were drawn in the morning after an o/n fast and again at 4 pm. Participants ate their normal meals and pursued normal hospital activities, while avoiding strenuous exercise. Serum creatinine concentration determined using the Jaffe method.	Creatinine concentration following usual meals in the late afternoon N = 72	Not applicable	Change in creatinine concentration	Ontario heart foundation, Toronto Western Hospital Medical Research Fund

Effect size

Change in creatinine concentration

In patients with inulin clearance ≥ 90 ml/min (N=38), the serum creatinine concentration was significantly greater in the afternoon than in the morning (after an o/n fast) (mean difference 0.087 mg/100ml, p<0.001). Similarly, patients with baseline serum creatinine concentration ≤ 1.4 mg/100ml (N=49) had a significantly greater serum creatinine concentration in the afternoon than in the morning (mean difference 0.092 mg/100ml, p<0.001).

By contrast, there was NS difference in serum creatinine concentration between morning and afternoon in patients with inulin clearance < 90 ml/min (N=34, mean difference 0.035 mg/100ml). Similarly, there was NS difference in serum creatinine concentration between morning and afternoon in patients with baseline serum

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
creatinine concentration > 1.4 mg/100ml (N=23, mean difference 0.000 mg/100ml).								

Table 246: 3922 [Shepherd et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shepherd J, Warner M, Kilpatrick E. Stabilty of creatinine with delayed separation of whole blood and implications for eGFR. Ann Clin Biochem. 2007; 44:1-4. Ref ID: 3922		N healthy volunteers = 5 N patients = 24 1 centre in UK	**Inclusion criteria:** sequentially recruited non-fasting volunteers (healthy and outpatients) age 27-64 years. **Exclusion criteria :** not stated **Population baseline characteristics:** Not stated	Effect of delay in centrifugation of blood samples on creatinine concentration determined by Kinetic Jaffe reaction. N=5 N=24 **Procedure:** Each subject provided six blood samples. Samples were kept at RT until centrifugation at 15 min, 4 h, 8 h, 14 h, 24 h, and 31 h-post collection. All samples were assayed for creatinine with 3 different kinetic Jaffe methods: Beckman DXC 800, Bayer Advia, Roche Modular P-800. The samples were also assayed for creatinine with 2 enzymatic assays: Roche- Modular P-800 enzymatic assay and Vitros 5.1 enzymatic assay. The between batch CV for each method was < 2% at a level of 100	Effect of delay in centrifugation of blood samples on creatinine concentration determined by enzymatic methods N=5 N=24	Not applicable	Change in eGFR with delay in centrifugation of blood sample Change in creatinine concentration with delay in centrifugation of blood sample	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				micromol/L. 24 patients provided two blood samples each. One sample of each pair was promptly centrifuged and assayed for creatinine (within 1 hour of receipt) by the kinetic Jaffe (DXC 800 autoanalyser). The other sample was left at RT and centrifuged up to 28 h later. eGFR was determined on each sample.				

Effect size

Effect of delayed centrifugation of blood samples on creatinine concentration:

Using 3 different kinetic Jaffe methods (Beckman, Bayer Advia, Roche), the creatinine concentration remained stable in blood (N=5 healthy volunteers, 30 samples total) up to 14 hours before centrifugation. A 24-h delay in centrifugation resulted in significant increases in creatinine concentration (mean difference Beckman DXC + 19.7 micromol/l ; Roche + 10.2 micromol/l ; Bayer Advia + 6.2 micromol/l, p<0.025).

Analysis of 24 pairs of blood samples taken from 24 patients showed NS difference in creatinine concentration before 10 h delay in centrifugation (p=0.46). Significant increases in creatinine concentration were seen after 10-24 h delay in centrifugation (P<0.001) (Beckman kinetic Jaffe method).

By contrast, the creatinine concentration remained stable, regardless of the delay in centrifugation, when assayed with enzymatic methods (N=5 healthy volunteers, 30 samples total; Roche, Vitros enzymatic methods).

Effect of delayed centrifugation of blood samples on the eGFR (determined from kinetic Jaffe Beckman DXC 800)

In 21 patients where the delay in centrifugation exceeded 10 h, the eGFR significantly decreased (p<0.001). This resulted in a change in CKD classification in 4 of these cases.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: authors recommend centrifugation of blood samples within 10 hours of receipt. Enzymatic methods show less variation, indicating that the instability of creatinine observed with the Jaffe method is not due to creatinine itself but to some other interfering factor (non-creatinine chromogen??)								

Q.5.2 Detection of blood and protein in the urine (2014 guideline – chapter 5.3)

Table 247: Ref ID: 309 [Agarwal et al. 2002]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Agarwal R, Panesar A, Lewis RR. Dipstick proteinuria: Can it guide hypertension management? American Journal of Kidney Diseases. 2002; 39(6):1190-1195. Ref ID: 309	Cross-sectional Diagnostic test: 1b + Single site renal clinic Indianapolis, USA	N =332	**Inclusions:** adults attending the renal clinic at the R.L. Roudebush Veterans Administration Hospital **Exclusion:** not stated **Baseline population:** Mean age: 66 years, 5% females, 39% hypertensive nephrosclerosis, 34% diabetic nephropathy, 10% glomerulonephritis, 3% renal obstruction, 3% unknown, 11% other causes of renal disease, average serum creatinine 2.7 mg/dl, CrCl (CG) 48 ml/min, mean BP 141/73 mm Hg, 56% taking ACE inhibitors or ARB	Multistix 10 SG (Bayer) reagent strip N= 332 **Protocol:** spot urine samples tested with Multistix 10 SG reagent strip (recorded as 0 to + 4) or quantitative method. Specific gravity was also recorded. Reagent strips were read on Clinitek 200+ automated reader.	Protein:creatinine ratio (PCR) of spot urine sample N= 332 **Protocol:** Total protein measured by a turbidometric assay using benzethonium chloride at 550 nm with a Hitachi analyzer. Creatinine measured by modified Jaffe reaction (Boehringer Mannheim). Urine protein:creatinine ratios were calculated.	N/A	Sensitivity Specificity Area under ROC	Not stated
Effect size Increasing specific gravity of urine predicted a decreasing protein:creatinine ratio. **Sensitivity**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

- At a cutoff of protein:creatinine ratio ≥ 1g/g creatinine, a Multistix reagent strip result of +1 gave a sensitivity of 96%.
- At a cutoff of protein:creatinine ratio ≥ 1g/g creatinine, a Multistix reagent strip result of +3 gave a sensitivity of 100%.
- At a cutoff of protein:creatinine ratio ≥ 3g/g creatinine, a Multistix reagent strip result of +1 gave a sensitivity of 100%.
- At a cutoff of protein:creatinine ratio ≥ 3g/g creatinine, a Multistix reagent strip result of +4 gave a sensitivity of 94%.

Specificity

- At a cutoff of protein:creatinine ratio ≥ 1g/g creatinine, a Multistix reagent strip result of +1 gave a specificity of 60%.
- At a cutoff of protein:creatinine ratio ≥ 1g/g creatinine, a Multistix reagent strip result of +3 gave a specificity of 87%.
- At a cutoff of protein:creatinine ratio ≥ 3 g/g creatinine, a Multistix reagent strip result of +1 gave a specificity of 46%.
- At a cutoff of protein:creatinine ratio ≥ 3 g/g creatinine, a Multistix reagent strip result of +4 gave a specificity of 83%.

Area under ROC

- At a cutoff of protein:creatinine ratio ≥ 1g/g creatinine, Multistix reagent strips had a significantly high diagnostic accuracy [AUC=0.945 (95% CI 0.922 to 0.966)]
- At a cutoff of protein:creatinine ratio ≥ 3g/g creatinine, Multistix reagent strips had a significantly high diagnostic accuracy [AUC=0.905 (95% CI 0.874 to 0.935)]

Note: population was mostly older males, reagent strips were read by an automated reader, and visual interpretation of reagent strip could change sensitivity/specificity.

Table 248: Ref ID: 341 [Arm et al. 1986]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arm JP, Peile EB, Rainford DJ et al. Significance of dipstick haematuria. 1. Correlation with microscopy of the urine. Br J Urol. 1986; 58(2):211-217. Ref ID: 3903	Study type Cross-sectional Diagnostic test 1b+	N participants = 100 Total N samples = 900 No. ITT 825 1 centre in UK	**Inclusion criteria:** adults admitted to hospital (not consecutively) with suspicion of hematuria **Exclusion criteria :** people unable to remain on the hospital ward for several days **Population baseline characteristics:** None stated	N-Multistix-SG reagent strip N samples = 825 **Procedure:** patients provided 3 urine samples/day for three days (9 samples/patient). Each sample was tested with N-Multistix-SG reagent strip and an aliquot was examined by phase contrast microscopy. Abnormal RBC count was defined as ≥ 10 RBC/microL	phase-contrast microscopy of un-spun urine N samples= 825	Not applicable	Sensitivity Specificity PPV NPV (Calculated by EC)	Not stated
Effect size When the reagent strip gave a negative result, 24.4% of the samples were found to be positive by microscopy (≥ 10 RBC/microL) PPV: When the reagent strip registered a "trace" result, 81.7% of the samples were found to be positive by microscopy (≥ 10 RBC/microL) PPV: When the reagent strip registered a "+" result, 100% of the samples were found to be positive by microscopy (≥ 10 RBC/microL) Calculated by EC: Sensitivity: 84.1% Specificity: 84.5%								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
PPV = 90% NPV = 75.6%								

Table 249: Ref ID: 158 [Brown et al. 1995]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brown MA, Buddle ML. Inadequacy of dipatick proteinuria in hypertensive pregnancy. Aust and NZ Journal of Obstetrics and Gynaecology 1995; 35: 366-369	Cross sectional study Diagnostic test 1b+	N=230 Consecutive patients	**Inclusion criteria:** pregnant women with hypertension, admitted to hospital for management of their hypertensive disorder. **Exclusion criteria:** not mentioned No baseline criteria reported. True proteinuria considered as ≥ 300 mg/day	Urinalysis using Multistix 10SG (Bayer Diagnostics) Three were done on a morning midstream urine sample before and after the 24 hour urine collection and on a well mixed aliquot of the 24 hour urine sample. 'Nil' and 'trace' proteinuria were considered to be negative.	24 hour urine protein measured by a benzethonium chloride turbidometric method (protein excretion ≥300mg/day considered proteinuria) Urine creatinine measured by the Jaffe method, Hitachi 911 autoanalyser (Boerhinger Mannheim)	n/a	PPV NPV	Division of Medicine, St Georges Hospital, Australia

Effect size:

Positive and negative predictive values of the three urine dipstick analyses compared with the 24 hour urine protein estimation in pregnant women with hypertensive disorders:

	PPV (%)	NPV (%)
Before 24 hour urine collection	86	38
After 24 hour urine collection	46	88
On aliquot from 24 hour urine collection	60	87

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Number of true positives 70/230 (30.4%) **Conclusions:** 'Nil' or 'trace' proteinuria misses significant proteinuria in 1 of 8 hypertensive pregnant women. A 24-hour collection should follow a '1+' or '2+' finding to be certain about the presence or absence of proteinuria. Assessment of potential bias: do not mention if the assessments were blinded to each other. Assessment of dipstick done by midwifery staff or by one of the investigators (on the aliquot of the 24 hour collection).								

Ref ID: 385 [Chan et al. 2005]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan RWY, Chow KM, Tam LS et al. Can the urine dipstick test reduce the need for microscopy for assessment of systemic lupus erythematosus disease activity? Journal of Rheumatology. 2005; 32(5):828-831. Ref ID: 385	Study type Cross-sectional Diagnostic test 1b+	Total N = 269 No. ITT 269 No. centres 1 centre in Hong Kong, China	**Inclusion criteria:** adults with systemic lupus erythematosus (SLE) **Exclusion criteria:** not stated **Population baseline characteristics:**		Hemastix reagent strip N samples = 269 **Procedure:** Patients were assessed for SLE Activity Index by an independent clinician. Spot urine sample collected and immediately tested with Hemastix (Bayer) and the result was scored as negative, nonhemolysed trace, nonhemolysed moderate, trace, small, moderate, or large for RBC. An aliquot of the same sample was removed for phase-contrast microscopy (400 x magnification) of the urinary sediment by an independent examiner blinded to the Hematsix test result.	phase-contrast microscopy of urinary sediment N samples= 269 Hematuria defined as ≥ 5 RBC/high power field. Urinary casts defined as the presence of heme-granular or RBC casts at 100X magnification.	Not applicable	Sensitivity Specificity Positive predictive value Negative predictive value Area under the ROC curve	Chinese University of Hong Kong research grants
				SLE					
			N	269					
			Mean Age, years (range)	37.6 (17-80)					
			% Female	96%					
			Mean SLE Activity Index score	6.1					

Effect size

Microscopic examination: 63/269 = 23% had hematuria and 21/269 = 8% had urinary casts

Hematuria Detection:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• Hemastix reagent strip identified 159/269 (59%) as having trace or more RBC. • Sensitivity: 98% • Specificity: 53% • Positive Predictive Value: 39% • Negative Predictive Value: 99% • Area Under the ROC (when trace RBC was defined as the cut-off): 0.97 **Urinary cast detection** • When a positive Hemastix reagent strip result was defined as trace or more RBC, • Sensitivity for detection or urinary casts: 91% • Specificity for detection or urinary casts: 44% • Positive Predictive Value: 12% • Negative Predictive Value: 98% • Area Under the ROC (when trace RBC was defined as the cut-off): 0.89 **Note:** High sensitivity for RBC detection but low specificity (high false positive rate).								

Table 250: Ref ID: 392 [Cortes-Sanabria et al.2006]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cortes-Sanabria L, Martinez-Ramirez HR, Hernandez JL, Rojas-Campos E, Canales-Munoz JL, Cueto-Manzano AM. Utility of the Dipstick Micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. Revisita de Investigacion Clinica 2006; 58(3): 190-197	Cross-sectional study Diagnostic test 1b + 3 health care units, Mexico	N=245	Mexican patients attending 3 primary health care units were randomly selected. **Inclusion criteria:** patients with type 2 diabetes with or without hypertension, patients with essential hypertension without diabetes type 2, of any age, sex and time since diagnosis. **Exclusion criteria:** cardiac failure, renal tract disease, acute febrile illnesses, urinary tract infection, hematuria, abnormal urinary sediment, any level of proteinuria in urinalysis and transitory albuminuria, secondary hypertension, serum creatinine ≥ 2 mg/dl.	Micraltest II dipstick (Roche diagnostics GmbH, Germany) performed on a first morning urine sample, ready by one investigator	24-h Nephelometry (Behring Nephelometer Analyzer II, Behring diagnostics GmbH, Germany) performed on a 24 hr urine collection, to which had been added the remainder of the first morning sample on which the Micraltest II had been performed.	n/a	Sensitivity Specificity PPV NPV Area under ROC	Not stated

Effect size

Performance of Micraltest II in compared with 24-h nephelometry in diabetic and hypertensive patients:

	Type 2 Diabetics (N=166)	Hypertensives (N=79)
Prevalence of albuminuria	42%	5%

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sensitivity			83%		75%			
Specificity			96%		95%			
PPV			95%		43%			
NPV			88%		99%			
Pearson correlation coefficient			0.81 (p<0.0001)		0.43 (p<0.0001)			
Mean area under ROC curve (95% CI)			0.91 (0.85-0.96)		0.85 (0.60-1.10)			
Best cut-off point value			30.5 mg/L		28.2 mg/L			
Sensitivity and PPV of the test increased with duration of diabetes and hypertension, as this increases the prevalence of albuminuria. **Assessment of bias** Blind comparison of test with reference standard. Patients apparently selected randomly but no mention of methods used for this.								

Table 251: Ref ID: 3859 [Gai et al. 2006]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gai M, Motta D, Giunti S et al. Comparison between 24-h proteinuria, urinary protein/creatinine ratio and dipstick test in patients with nephropathy: Patterns of proteinuria in dipstick-negative patients. Scandinavian Journal of Clinical & Laboratory Investigation	Cross-sectional Diagnostic test: 1b+ Single nephrology laboratory, Italy	N = 297	**Inclusions:** consecutive patients with different kidney diseases referred to nephrology lab from outpatient department between Jan.-April, 2003. **Exclusion:** not stated **Baseline population:**		Multistix 10 SG (Bayer) reagent strip Protein:Creatinine Ratio (PCR) N= 297 **Protocol:** second midstream morning urine samples were collected and tested with Multistix reagent strip. Multistix detects albumin at 0, 15, 30, 100, and ≥ 300 mg/dl; sensitivity range 15-30 mg/dl. Reagent strips were read on Clinitek 200. Protein:creatinine ratio of the urine sample was	24-hour protein excretion N= 297 **Protocol:** patients submitted a 24-h timed urine collection and protein was measured using the pyrogallol red-molybdate method	N/A	Test correlation Sensitivity Specificity Area under ROC	Not stated
			N	**297**					
			Mean age, years (range)	51.7 (14-89)					
			median plasma creatinine, micromol/l (range)	106 (44-946)					
			% chronic nephropathy	38					
			% glomerulonephritis/vasculitis	23					
			%	8.5					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
. 2006; 66(4):299-308. Ref ID: 3859			nephrolithiasis		determined on the Synchron CX9 ALX by measuring protein concentration (pyrogallol red-molybdate method) and creatinine by the Jaffe method (picric acid under alkaline conditions)				
			% hypertensive nephropathy	8					
			% acute pyelonephritis	7.5					
			% chronic pyelonephritis	6.5					
			% other	8.5					

Effect size

The overall prevalence of proteinuria was 62.3% (median 0.56 g/24-h; range 0.010-16.99 g/24-h)

0.150 g/24-h was the cut-off used to discriminate between physiological and pathological proteinuria.

Test correlation:

Compared to the reference test (24-h protein), there was a significantly high correlation with protein:creatinine ratio (R=0.82, p<0.0001).

Compared to the reference test (24-h protein), there was a significantly high correlation (but lower than that of PCR) with Multistix reagent strip testing (R=0.75, p<0.0001)

The correlation between PCR and Multistix reagent strip testing was R=0.72, p<0.0001.

Sensitivity

Compared with 24-h protein (cut-off 0.150 g/24-h), Multistix reagent strip testing had a sensitivity of 49.2%.

Compared with 24-h protein (cut-off 0.150 g/24-h), protein:creatinine ratio had a sensitivity of 91.4%.

Specificity

Compared with 24-h protein (cut-off 0.150 g/24-h) , Multistix reagent strip testing had a specificity of 93.8%.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Compared with 24-h protein (cut-off 0.150 g/24-h), protein:creatinine ratio had a specificity of 75%. **Area under ROC** Using the 24-h protein as a reference, the protein:creatinine ratio had significantly higher diagnostic accuracy [AUC=0.840 (95% CI 0.791 to 0.889)] compared with Multistix reagent strip testing [AUC=0.778 (95% CI 0.722 to 0.834), p<0.0001]. **Note:** authors favour PCR over reagent strips.								

Table 252: Ref ID: 3864 [Gilbert et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gilbert RE, Akdeniz A, Jerums G. Detection of microalbuminuria in diabetic patients by urinary dipstick. Diabetes Research and Clinical Practice 1997; 35: 57-60	Cross-sectional Diagnostic test 1b+ 1 centre: Australia	N=411	Consecutive diabetic outpatients recruited for the study, at an endocrinology unit in Australia. No further detail given on the patient population. No exclusion criteria mentioned.	Micral-Test II (Boehringer-Mannheim, Mannheim, Germany) Both tests performed on a 24-hr urine specimen collected from each patient.	Urinary albumin concentration as determined by radioimmunoassay (using a double antibody method with a detection limit of 16 µg/l and intra- and inter assay coefficients of variation of 1.8 and 7.6% respectively, for a concentration of 20 mg/l).	n/a	Sensitivity Specificity PPV False positives False negatives	Boehringer Mannheim

Effect size

Performance of Micral-Test II in detecting UAC>20 mg/l compared with radioimmunoassay detection in diabetic patients:

Sensitivity	93%
Specificity	93%
PPV	89%
False positives	7%
False negatives	7%
Area under ROC curve	0.95

In this study prevalence of microalbuminuria 28% and abnormal albuminuria (micro-and macroalbuminuria) 39%.

Change in the prevalence of abnormal albuminuria to ~20% would decrease the PPV of the Micral-Test II to 81%.

Assessment of potential bias:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Each Micral-Test II strip read by two scientists independently with 99% agreement. Do not mention if comparison between test and reference is blind.								

Table 253: Ref ID: 3937 [Highby et al. 1995]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Higby K, Suiter CR, Siler-Khodr T. A comparison between two screening methods for detection of microproteinuria. American Journal of Obstetrics and Gynaecology 1995; 173: 1111-1114	Cross sectional study Diagnostic test 1b+ 2 teaching institutions in Texas, USA	N=401 given N=690 specimens	**Inclusion criteria:** low and high risk patients seen for prenatal care **Exclusion criteria:** not mentioned **Baseline characteristics:** not mentioned	Multistix 10SG (minimum threshold 15 mg/dl) Micro-bumintest (Miles Diagnostic Division) (minimum threshold 4 mg/dl)	24 hour urine protein (measured with a pyrogallol red-molybdate complex reaction)	n/a	Sensitivity Specificity PPV NPV	Not mentioned.

Effect size:

Validation of thresholds for both tests (N=690)

	Micro-bumintest (≥4 mg/dl)	Multistix 10SG (≥15 mg/dl)
Sensitivity	87	36
Specificity	99	97
PPV	81	68
NPV	99	88

Likelihood ratios for both tests:

	LR for a positive result	LR for a negative result
Micro-bumintest	66.6	0.134
Multistix 10SG	10.42	0.658

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Assessment of potential bias: Dipstick tests were done in a blinded manner by the same investigator to eliminate interobserver variability. Do not mention if dipstick and 24 hour urine sample were blinded.								

Table 254: Ref ID: 173: [Meyer et al. 1994]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Meyer NI, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe protein. American Journal of Obstetrics and Gynaecology 1994; 170: 137-141	Cross-sectional study, retrospective record review. Diagnostic test. 1b+ Recruited from hospital admissions in USA	N=300	**Inclusion criteria:** pregnant women with hypertensive disease in pregnancy who had a minimum of 2 urine dipstick protein determinations at least 6 hours apart as well as a 24 hour urine collection. **Exclusion criteria:** if samples were collected postpartum. **Baseline characteristics:** Mean age 23.2 (SD 6.3) years	Urine dipstick (not specified which)	24 hour total urinary protein excretion	n/a	Sensitivity Specificity PPV NPV Accuracy	Not mentioned

Effect size:

Result	Urine dipstick ≥ 1+ Protein excretion ≥ 300 mg/24hr	Urinary dipstick ≥ 3+ Protein excretion ≥ 300 mg/24hr
Sensitivity	67	75
Specificity	74	81
PPV	92	36
NPV	34	96

Conclusions: A dipstick of negative to trace should not be used to rule out significant proteinuria (NPV 34%). Urine dipstick values of 3+ to 4+ should not be used to diagnose severe pre-eclampsia as their PPV is only 36%

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Assessment of potential bias: Not mentioned whether the assessments were blinded to each other. Selection bias in record review.								

Table 255: Ref ID: 3936 [Paruk et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Paruk F, Moodley J, Daya PKS, Meineke K. Screening for proteinuria in hypertensive disorders of pregnancy. Journal of Obstetrics and Gynaecology 1997; 17 (6): 528-530	Cross-sectional study Diagnostic test 1b + Inpatients recruited from a tertiary public sector hospital	N=150	**Inclusion criteria:** pregnant patients with hypertensive disorder (defined as a diastolic blood pressure ≥90 mmHg documented on 2 separate occasions at least 4 hours apart). **Exclusion criteria:** not mentioned **Baseline characteristics:** Mean age 26.6 (SD 6.6) years Systolic BP 143 (SD 12) mmHg Diastolic BP 95 (SD 5) mmHg Gestation 30 (SD 5) weeks	Dipstix analysis (Multistix-AMES) performed at random and at 6 and 12 hours into the 24 hour urine collection a 5ml aliquot was collected	24 hour urine protein (Beckman Synchron)	n/a	Sensitivity Specificity PPV NPV Accuracy	Not mentioned

Effect size:

Urine dipstick compared with 24 hour urine analysis (%)

Number of true positives: 84/150 (56%)

Result	Random dipstick	Hour 6 dipstick
Sensitivity	84	84.5
Specificity	61	90.1
PPV	57	84.5
NPV	86	90.0

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Accuracy			69		87.9			
Conclusions: random urinary dipstick is unreliable in screening for proteinuria in hypertensive disorders of pregnancy. A 6-hr collection is much more accurate. **Assessment of potential bias:** Do not report if comparison between test and reference is blind, or if random and 6 hour test were blinded or independent of each other.								

Table 256: Ref ID: 523 [Pugia et al. 2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pugia MJ, Wallace JF, Lott JA et al. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. Journal of Clinical Laboratory Analysis. 2001; 15(5):295-300. Ref ID: 523	Cross-sectional Diagnostic test: 1b+ 4 hospital study: USA	N total =666	**Inclusions:** hospitalised patients or healthy volunteers **Exclusion:** not stated **Baseline population:** Not stated	Multistix PRO (Bayer) reagent strip N= 666 **Protocol:** urine samples were collected and tested within 1 hour (or frozen if analysis was delayed) with reagent strip or quantitative method. Specimens were measured in duplicate with Multistix PRO. Multistix PRO detects ≥ 80 mg/l albumin and ≥ 300 mg/l protein and ACR ≥ 80 mg/g creatinine or PCR ≥ 300 mg/g creatinine. Dipsticks were read on Clinitek 50 reflectometer.	Immunonephelometric measure of albumin Total protein measured by pyrogallol red method Creatinine measured by rate-Jaffe N= 666	N/A	Positive Predictive Value (PPV) Negative Predictive Value (NPV)	Not stated
Effect size Cut-off values albumin ≤ 80 mg/l Cut-off values protein ≤ 300 mg/l Cut-off values ACR ≤ 80 mg/g creatinine Cut-off values PCR ≤ 300 mg/g creatinine								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Diagnostic Accuracy of Multistix PRO compared to quantitative analysis for albumin, protein, ACR, and PCR								

Population	N	PPV (albumin)	NPV (albumin)	PPV (ACR)	NPV (ACR)	PPV (protein)	NPV (protein)	PPV (PCR)	NPV (PCR)
Healthy volunteers	129	-	100	-	100	-	100	-	100
General Hospital population	310	82	99	84	89	67	95	84	87
Kidney disease	113	84	97	86	100	72	91	92	93
Diabetics	80	75	100	83	100	46	100	83	98
Cardiovascular Disease	48	82	100	85	87	79	95	96	91
Cancer	31	43	100	43	100	57	89	71	94

84 samples were dilute (creatinine ≤ 250 mg/l) and assay of albumin or protein in dilute urine samples is unreliable, even when the ratio to creatinine is used. More dilute samples were identified by Multistix PRO than by quantitative methods.

Table 257: Ref ID: 135 [Saudan et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. British Journal of Obstetrics and Gynaecology 1997; 1.4: 1159-1164	Cross-sectional study Diagnostic test 1b+	N=103 samples	Inclusion criteria: pregnant women admitted to hospital or pregnancy day assessment unit Exclusion criteria: not mentioned Baseline characteristics: not mentioned	Multistix 10SG (Bayer Diagnostics, Australia) Automated urinalysis (Clinitek 100 Ames)	Urine protein concentration Urine protein creatinine ratio	n/a	Sensitivity Specificity PPV NPV	Division of Medicine and South path Pathology services, St Georges hospital.

Effect size:

Visual dipstick urinalysis compared with urine protein concentration measurement

	Negative/trace	1+ (0.3g/L)	2+ (1g/L)	3+/4+ (≥3g/L)	Overall
Sensitivity		100	100	100	100
Specificity		62	85	98	55
PPV		24	53	93	
NPV	100				

Other analyses in this study were of the automated urinalysis compared with the urine protein concentration and urine protein concentration compared with a 24 hour urine collection, but these results are not presented here.

Assessment of bias: do not mention if recruitment was random or consecutive. Also no mention of whether assessments of samples were blinded.

Table 258: Ref ID: 3881 [Waugh et al. 2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Waugh J, Bell SC, Kilby M, Lambert P, Shennan A, Halligan A. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. Hypertension in Pregnancy 2001; 20(2): 205-217	Cross sectional Diagnostic test 1b+ 1 centre, Leicester, UK	N=197	Pregnant women presenting for assessment of hypertension in pregnancy or as referrals to a hypertension clinic, > 20 weeks gestation, hypertension defined as SBP > 140 mm Hg DBP > 90 mm Hg on two occasions or DBP > 110 mm Hg on one occasion No exclusion criteria reported Baseline data: mean age was 27 years (range 18-36 years), 36 weeks gestation, 87% Caucasian, Median SBP 145 mm Hg, median DBP 90 mm Hg	BM-Test-5L test strips (Boehringer Mannheim UK, East Sussex) applied to a 10 ml aliquot of thoroughly mixed 24-hr urine collection	Benzethonium Chloride assay Bradford assay Both performed on an aliquot of thoroughly mixed 24-hr urine collection	n/a	Sensitivity Specificity PPV NPV Prevalence of proteinuria	Not stated

Effect size

Using the dipstick, proteinuria is defined as ≥1+ where the threshold of sensitivity is set as 0.3 mg/ml.

In the assays, the definition of significant proteinuria based on total protein excretion in 24h is most commonly accepted as ≥ 0.3g/24h.

Prevalence of proteinuria:

	≥0.3mg/ml (95% CI)	≥0.3g/24h (95% CI)
Dipstick	16.2% (11.4-22.2)	
Benzethonium Chloride1	54.3% (47.1-61.4)	70.1% (63.1-76.4)
Bradford assay1	21.8% (16.3-28.3)	24.9% (19.0-31.5)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

1Using both definitions of a true positive result for proteinuria, these prevalences were significantly different from that generated by the dipstick test.

Comparison of performance of dipstick urine analysis with Benzethonium Chloride and Bradford assay based on the definition of a true positive result for proteinuria used in the assays:

	≥0.3 g/24h		**≥0.3 mg/ml**	
	Benzethonium Chloride	Bradford assay	Benzethonium Chloride	Bradford assay
Sensitivity	22.5% (15.8-30.3)	57.1% (42.2-71.2)	29.0% (20.6-38.5)	69.8% (53.9-82.8)
Specificity	98.3% (90.9-99.9)	97.3% (93.2-99.3)	98.9% (94.0-99.9)	98.7% (95.4-99.8)
NPV	35.2% (27.9-43.0)	87.3% (81.2-91.9)	53.9% (46.0-61.7)	92.1% (86.9-95.7)
PPV	96.9% (83.8-99.9)	87.5% (71.0-96.5)	96.9% (83.8-99.9)	93.8% (79.2-99.2)

Assessment of bias:

Dipstick test performed by one trained observer.

Not mentioned if reference test was blinded to dipstick result.

Table 259: Ref ID: 459: Konta et al. 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, Ikeda A, Ichikawa K, Kato T, Kawata S, Kubota I. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. Clin Exp Nephrology 2007; 11: 51-55	Cross sectional study Diagnostic test II + Japanese cross-sectional health survey	N=2321 N=2401 in original study, N=80 excluded for incomplete data	Patients recruited from the general population of Takahata, Japan. Sampling and recruitment methods, inclusion criteria not described in this paper. **Exclusion criteria:** patients with incomplete data, women menstruating. **Baseline characteristics** Men 44.5% Mean age 64 years Range (40-87 years)	Urinalysis by dipstick (Ames Multistix, Bayer Diagnostic, Victoria, Australia) Reagent strip and reference test (ACR) determined on an early morning spot urine specimen, collected after an overnight fast. Results of reagent strip recorded as -, trace, 1+, 2+, 3+.	Urinary albumin:creatinine ratio (ACR) Urine albumin determined by immunoturbidometry Serum creatinine measured by an enzymatic method.	n/a	Prevalence of microalbuminuria in dipstick trace proteinuria Sensitivity Specificity PPV NPV Analysis by subgroups: gender, age, presence of co-morbid conditions	Japanese society for the Promotion of Science and the Ministry of Education, Science, Sports and Culture, Japan.

Effect size

Albuminuria defined as ACR ≥ 30 mg/g creatinine

Overall dipstick diagnostic performance

	Dipstick test **Trace proteinuria defined as positive for albuminuria**	**Dipstick test** **Conventional definition for albuminuria of ≥ 1+**
Sensitivity %	37.1	23.3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Specificity %			97.3		98.9			
PPV %			71.4		79.8			
NPV %			89.5		87.7			

Dipstick diagnostic performance: Subgroup analyses. Values are performance calculated by new definition "trace proteinuria" (conventional definition ≥ 1+ on reagent strip)

	Men	Women	40-59 years	>60 years	Diabetes (N=201)	Hypertension (N=1323)
Sensitivity %	53.2 (34.5)	22.2 (13.0)	43.7 (28.2)	33.1 (19.3)	45.1 (33.8)	37.0 (24.1)
Specificity %	98.4 (99.5)	96.5 (98.5)	95.6 (98.2)	98.3 (99.4)	97.9 (98.5)	97.7 (99.1)
PPV %	86.7 (93.7)	51.3 (58.5)	50.0 (60.6)	80.5 (86.9)	91.4 (92.3)	80.6 (87.8)
NPV %	91.4 (88.5)	88.1 (87.1)	94.4 (93.1)	87.1 (84.9)	76.5 (73.1)	85.8 (83.6)

Potential sources of bias:

Not mentioned if there was blinding of in comparison of dipstick and reference standard.

Table 260: Ref ID: 341 [Chandhoke et al. 1988]

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chandhoke PS, McAninch JW. Detection and significance of microscopic hematuria in patients with blunt renal trauma. Journal of Urology. 1988; 140(1):16-18.	Study type Cross-sectional Diagnostic test 1b- Poor methodology No detail on blinding, or when the two tests were done, or in what order. No presentation of sensitivity/specificity in the results section (only in the abstract)	Total N = 339 No. ITT 339 No. centres 1 centre in California, USA	**Inclusion criteria:** adults with blunt renal trauma who underwent subsequent renal imaging (excretory urography or CT and/or angiography) **Exclusion criteria:** not stated **Population baseline characteristics:**None stated	Chemstrip 8 reagent strip N samples = 339 **Procedure:** Urine sample obtained by voiding or Foley catheterisation was tested with Chemstrip 8 reagent strip for presence of RBC.	phase-contrast microscopy of urinary sediment N samples= 339	Not applicable	Sensitivity Specificity	Not stated
Effect size: Chemstrip 8 reagent strip for detecting microscopic hematuria: > 97.5% Sensitivity > 97.5% specificity								

Table 261: Ref ID: 174 [Gleesone et al. 1993]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gleeson MJ, Connolly J, Grainger R et al. Comparison of reagent strip (dipstick) and microscopic haematuria in urological out-patients. British Journal of Urology. 1993; 72(5:Pt 1):t-6. Ref ID: 174	Cross-sectional Diagnostic test: II – (no gold standard test comparison: not phase contrast but light microscopy, poor methodology, no detail on blinding, when the 2 tests were performed, little detail on test population) Single center study: Dublin, Ireland	N =1000	**Inclusions:** urological outpatient urine samples between July-Nov., 1990 **Exclusion:** not stated **Baseline population:** No detail given only that 570 males and 258 females (mean age 50 years) provided urine samples	B.M. dipstick (Boehringer Mannheim GmbH) N= 1000 **Protocol:** midstream urine samples collected and tested with BM reagent strip for red blood cells (RBC) with results reported as negative, trace, +1, +2, +3, or +4.	Light microscopy for RBC to detect haematuria N= 1000 **Protocol:** Light microscopy of un-spun urine sample. Haematuria defined as ≥ 5 RBC/microL on a Kova Glasstic Slide.	N/A	Sensitivity Specificity	Not stated
Effect size Sensitivity of reagent strip to detect haematuria: 86% Specificity of reagent strip to detect haematuria: 85% Note: authors acknowledge that they did not use phase contrast microscopy as the gold standard. Standard light microscopy can miss RBC, but they note that phase contrast microscopy is not readily available (1993).								

Q.5.3 Urinary albumin:creatinine and protein:creatinine ratios, and their relationship to 24 hour urinary protein (2014 guideline – chapter 5.4)

Q.5.3.1 What are the benefits in terms of accuracy and cost in measuring albumin:creatinine ratio versus protein:creatinine ratio to quantify proteinuria in adults with CKD?

Table 262: Ref ID: 269 [Chaiken et al.1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chaiken RL, Khawaja R, Bard M et al. Utility of untimed urinary albumin measurements in assessing albuminuria in black NIDDM subjects. Diabetes Care. 1997; 20(5):709-713.	Study type Cross-sectional Diagnostic test 1b + No. centres: 1 Chicago, USA	Total N = 123 No. ITT 123	**Inclusion criteria:** Black patients with NIDDM attending the diabetic clinic at Kings County Hospital, Chicago, USA, from Sept. 1993 to May 1995. Patients were normotensive or hypertensive (≥140/90 mm Hg or mean arterial pressure ≥ 106)) **Exclusion criteria**: None stated. **Population baseline characteristics:** Provided for the whole study (218, but not for the 123 patients that provided both a 24-h and random urine sample).	Random urinary albumin:creatinine ratio No. of patients 123 **Procedure:** The random urine sample was provided on the day that the 24-h urine collection was brought to the clinic. Urinary creatinine was measured by a modified Jaffe reaction (by Slot). Urinary albumin concentration was assayed with the Diagnostics Products double-antibody albumin kit.	24-h urinary albumin excretion No. of patients 123 **Procedure:** 123 patients provided a 24-h urine collection.	Not applicable	Test correlation	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size: **Test Correlation** In the total population (N=123), there was a significantly high correlation between random urine albumin:creatinine ratio and 24-h albumin excretion rate (r=0.96, p =0.0001). In subgroup analysis of patients with clinical proteinuria (albumin:creatinine ratio >300 microgram/mg) (N=7), the correlation between random urine albumin:creatinine ratio and 24-h albumin excretion rate was significantly high (r=0.92, p=0.003). In subgroup analysis of patients with microalbuminuria (albumin:creatinine ratio 30 to 300 microgram/mg) (N=26), the correlation was much lower (r=0.55, p=0.005). In patients with an albumin:creatinine ratio < 30 microgram/mg (normal range) (N=90), the correlation between random urine albumin:creatinine ratio and 24-h albumin excretion rate was lower (r=0.59, p<0.0001).								

Table 263: Ref ID:48: [Gansevoort et al. 2005]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gansevoort RT, Verhave JC, Hillege HL et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney International - Supplement. 2005;(94):S28-S35.	Study type Cross-sectional Diagnostic test 1b + No. centres 1, Netherlands	Total N = 2527 No. ITT 2527	**Inclusion criteria:** A representative population of Netherlands recruited for the PREVEND trial (Prevention of Renal and Vascular End-stage Disease). **Exclusion criteria:** Urinary tract infection, Type 1 diabetes, pregnancy, proteinuria **Population baseline characteristics:**		Spot morning urinary albumin:creatinine ratio No. of patients 2527 **Procedure:** Patients provided a spot morning urine sample. Urinary creatinine was measured by an automatic enzymatic method (Kodak Ektachem dry chemistry).	24-h urinary albumin excretion No. of patients 2527 **Procedure:** On average 77 days after providing the spot morning urine sample, subjects were instructed to collect 24-h urine on two consecutive days. Measurements of urinary volume, albumin, and creatinine were	Not applicable	Sensitivity Specificity Area under the ROC	Not stated.
			N total	2527					
			% Male	47.1					
			Mean age, years	48.8					
			Mean weight, kg	77.2					
			% Caucasian	95.4					
			% CVD history	11.4					
			% Type 2 diabetics	2.6					
			Median spot morning albumin:creatinine ratio, mg/g	4.9					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Median 24-h urinary albumin excretion rate, mg/24-h	7.0		performed on each collection. Urinary albumin excretion was determined by nephelometry. Urinary albumin excretion rate was calculated as the average of the two consecutive 24-h urine collections.			

Effect size			
Urine test to identify albumin excretion rate > 30 mg/24-h	% Sensitivity (95% CI)	% Specificity (95% CI)	Area under the Curve
Spot morning urine albumin:creatinine ratio > 30 mg/g	49.0 (71.1 -56.9)	98.7 (98.2-99.1)	Not stated
Spot morning urine albumin:creatinine ratio > 9.9 mg/g (discriminator value)	87.6 (82.4 – 92.8)	87.5 (86.2 -88.9)	0.93

A spot morning albumin:creatinine ratio > 30 mg/g had a low sensitivity and high specificity (49% and 98.7%, respectively) of predicting an albumin excretion rate of > 30 mg/24-h. Furthermore, by dropping the cutoff to 9.9 mg/g (the value on the ROC curve that intersects the 100% sensitivity, 100% specificity diagonal), the sensitivity increased but the specificity decreased (87.6% and 87.5%, respectively).

Table 264: Ref ID: 486 [Gatling et al. 1988]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gatling W, Knight C, Mullee MA et al. Microalbuminuria in diabetes: A population study of the prevalence and an assessment of three screening tests. Diabetic Medicine. 1988; 5(4):343-347.	Study type Cross-sectional Diagnostic test 1b + No. centres Not stated; Poole, UK	Total N = 842 No. ITT 311	**Inclusion criteria:** 842 diabetic patients registered at 40 local GPs were interviewed by a single observer (WG). Patients were classified as insulin dependent diabetics if they had documented ketoacidosis or been continuously treated with insulin, except for a break of 1 month. All other diabetics were classified as non-insulin dependent diabetics. **Exclusion criteria:** Urinary tract infection, proteinuria **Population baseline characteristics:**		2 interventions Random urinary albumin:creatinine ratio Overnight urinary albumin:creatinine ratio No. of patients 311 **Procedure:** Patients provided freshly voided midstream random urine samples. These were assayed for proteinuria (excluded) and UTI (excluded). An aliquot of each	Timed overnight urinary albumin excretion No. of patients 311 Procedure Patients provided timed overnight urine collections within 2 weeks of the interview with WG. Urinary albumin was	Not applicable	Test correlation Sensitivity Specificity Predictive value	Wessex Regional Health Authority Research Fund, the Bournemouth Lions, Wellcome Foundation, and Bayer UK Limited.
			N total	842					
			N Insulin dependent diabetics	202					
			N Insulin dependent diabetics	640					
			Age range, years	5 -98					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Duration of diabetes, years	0-58	sample was frozen for later (3 months) measurement of albumin and creatinine. Urinary albumin was measured by a micro-ELISA technique and creatinine was measured by a modified Jaffe method. **Caveat:** Compliance with submitting overnight timed urine sample was poor (59%) and after exclusions for UTI and proteinuria, this gave data for only 311/842 patients.	measured by a micro-ELISA technique			
Effect size **Test Correlation** In 311 patients, there was a significant correlation between random urine albumin:creatinine ratio and overnight albumin excretion rate (Kendall's correlation									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

coefficient tau-b, r=0.32, p < 0.001). Kendall's tau-b (a non-parametric assessment of the correlation) was used because the distribution of results was not normal.

Comparing the overnight albumin excretion rate to overnight albumin:creatinine ratio (N=446), there was a significantly higher correlation (Kendall's correlation coefficient tau-b, r=0.71, p < 0.001).

Urine test to identify albumin excretion rate > 30 microgram/min	Number of samples	Sensitivity (%)	Specificity (%)	Predictive Value (%)
Random albumin:creatinine ratio > 3.0 mg/mmol	311	80	81	12
Overnight albumin:creatinine ratio > 3.5 mg/mmol	441	88	99	72
Overnight albumin:creatinine ratio > 2.0 mg/mmol	441	96	100	35

A random albumin:creatinine ratio > 3.0 mg/mmol had a sensitivity and specificity (80% and 81%, respectively) of predicting an albumin excretion rate of > 30 microgram/min. It had a poor predictive value of only 12%.

An overnight albumin:creatinine ratio > 3.5 mg/mmol had a sensitivity and specificity (88% and 99%, respectively) of predicting an albumin excretion rate of > 30 microgram/min. It had a better predictive value of 72%. Furthermore, by dropping the cutoff to 2.0 mg/mmol, the sensitivity and specificity increases (96% and 100%, respectively), but the predictive value is lower (35%).

The authors favour the use of measuring the albumin:creatinine ratio in an early morning urine sample. They are equating overnight with early morning.

Table 265: Ref ID: 516 [Hutchison et. al. 1988]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hutchison AS, O'Reilly DSJ, MacCuish AC. Albumin excretion rate, albumin concentration, and albumin/creatinine ratio compared for screening diabetics for slight albuminuria. Clinical Chemistry. 1988; 34(10):2019-2021.	Study type Cross-sectional Diagnostic test 1b + No. centres 1 Glasgow, Scotland	Total N = 261 No. ITT 261	**Inclusion criteria** Diabetic patients attending the diabetic clinic at Glasgow Royal Infirmary. No deliberate selection process used. **Exclusion criteria** Clinical nephropathy (persistent proteinuria defined as Albustix-positive, urine protein excretion > 500 mg/24 h) **Population baseline characteristics:** Not stated.	Overnight (First morning) urinary albumin:creatinine ratio No. of patients 261 **Procedure** Patients were asked to note the time of their last micturition before retiring and then to collect all of the next urine sample passed, again noting the time. An aliquot of this was considered equivalent to the first morning urine specimen. Specimens were stored at 4ºC and	Timed overnight urinary albumin excretion No. of patients 261 **Procedure** Same as for intervention.	Not applicable	Test correlation Sensitivity Specificity Positive Predictive value Negative Predictive value	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				were analysed within 4 weeks. Urinary creatinine was measured by a modified Jaffe reaction on an AutoAnalyzer II. Between batch CV was < 4%. Urinary albumin concentration was measured with a competitive binding radioimmunoassay.				

Effect size

Test Correlation

In 261 patients, there was a high correlation between first morning urine albumin:creatinine ratio and overnight albumin excretion rate (r=0.921, p not given).

Urine test to identify albumin excretion rate > 30 microgram/min	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
First morning albumin:creatinine ratio > 3.0 mg/mmol	96.8	93.9	68.2	99.5

Sensitivity is the proportion of AERs > 30 correctly identified by the screening test.

Specificity is the proportion of AERs < 30 correctly excluded by the test.

Positive predictive vale is the proportion of true positives in the sample.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Negative predictive value is the proportion of true negatives in the sample. The authors favour the use of measuring the albumin:creatinine ratio in an early morning urine sample. They are equating overnight with early morning.								

Table 266: Ref ID: 4121 [Jafar et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jafar TH, Chaturvedi N, Hatcher J et al. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population.[see comment]. Nephrol Dial Transplant. 2007; 22(8):2194-2200. Ref ID: 4121 .	Study type Cross-sectional Diagnostic test 1b + multicentre: Pakistan	Total N = 577	**Inclusion criteria:** adults ≥ 40 years old sampled from four randomly selected communities in Karachi **Exclusion criteria :** pregnancy, heavy exercise (> 1h on the day of the urine collection), mentally incompetent, bed-ridden people **Population baseline characteristics:** Median AER = 4.8 mg/day Median ACR = 5.0 mg/g N=314 women N=263 men	Random urinary albumin:creatinine ratio No. of patients 577 **Procedure** The spot morning urine sample was collected within 2 days of the 24-h urine collection. Laboratory tests (fasting blood glucose, serum and 24-h urine creatinine, urine albumin), BP, and health questionnaire given to each subject.	24-h urinary albumin excretion (UAE) No. of patients 577	Not applicable	Sensitivity Specificity AUC P30	Wellcome Trust UK
Effect size Albuminuria defined as UAE ≥ 30 mg/24-h. Prevalence of albuminuria in the Indo-Asian sample was 11.8% P30: The proportion of estimates of ACR within 30% of the UAE was 33% **Area Under the ROC:**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
For men, the AUC for ACR to detect albuminuria was 0.90 (95% CI 0.86 to 0.93) For women, the AUC for ACR to detect albuminuria was 0.86 (95% CI 0.82 to 0.89) **Sensitivity** For men, the sensitivity for ACR (at a cut-off of 30 mg/g) to detect albuminuria was 60% For women, the sensitivity for ACR (at a cut-off of 30 mg/g) to detect albuminuria was 46% **Specificity:** For men, the specificity for ACR (at a cut-off of 30 mg/g) to detect albuminuria was 97% For women, the specificity for ACR (at a cut-off of 30 mg/g) to detect albuminuria was 95% The positive predictive value for albuminuria in those with high ACR (≥ 30 mg/g) was 72% The negative predictive value for albuminuria in those with high ACR (≥ 30 mg/g) was 95%								

Table 267: Ref ID: 957 [Rodby et al. 1995]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rodby RA RRS. The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1995; 26(6):904-909.	Study type Cross-sectional Diagnostic test 1b +	Total N = 229 No. ITT 229 No. centres Not stated; US.	**Inclusion criteria:** 229 Type I diabetic adults with overt nephropathy and clinical proteinuria screened for participation in the Collaborative Study Group's clinical trial of "Angiotensin-Converting Enzyme Inhibition in Type I Diabetic Nephropathy" **Exclusion criteria** Not stated **Population baseline characteristics:** Mostly stated elsewhere (Bain et al., 1992)		Urinary protein:creatinine ratio No. of patients 229 **Procedure:** Patients provided random urine samples at the clinic. Protein concentration was determined using the Ponceau S/trichlororoacetic acid method calibrated against a human serum albumin standard. Creatinine concentration was measured by the modified Jaffe rate method on a Beckman Creatinine Analyzer II. The urine protein:creatinine ratio was obtained by	24-h urinary protein excretion No. of patients 229 **Procedure:** 177 patients provided 24 hour urine collections the day before the scheduled clinic visit. Urine collection began immediately after completion of the first morning void and urine samples were then collected for 24 h, including the final void at the completion of the 24 h period.	Not applicable	Test correlation Precision	US Public Health Service and Bristol-Myers Squibb Pharmaceutical Research Institute
			N	229					
			Mean duration of insulin dependence, years	21					
			Mean urinary protein excretion (SD), g/24	2.3 (2.5)					
			Mean serum creatinine (SD)	1.6					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			mg/dL	(1.0)	dividing the urinary protein concentration by the urine creatinine concentration.				
			Mean age (SD), years	37 (8)					
			% men	52					

Effect size

Test Correlation

In 229 patients, log-log transformation of the data showed a high correlation between random urine protein:creatinine ratio and 24 h urinary protein excretion rate (r=0.90, p not reported). The slope of the regression line (m=0.9) was almost identical to the line of unity (m=1), therefore protein:creatinine ratio was an excellent estimate of 24 h urinary protein excretion.

Precision

Standard deviation around the regression line increased as the protein:creatinine ratio increased. The confidence intervals are large and increase as the protein:creatinine ratio increases. This means that the protein:creatinine ratio becomes a less precise predictor of 24 h urinary protein excretion in the higher ranges of urinary protein excretion.

Table 268: Ref ID: 655 [Ruggenenti et al. 1998]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ruggenenti P, Gaspari F, Perna A et al. Cross sectional longitudinal study of spot morning urine protein: Creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. British Medical Journal. 1998; 316(7130):504-509. Ref ID: 655	Study type Cross-sectional Diagnostic test 1b + No. centres 1 centre in Italy	Total N = 177 No. ITT 177	**Inclusion criteria** 177 non-diabetic adults with CKD and persistent clinical proteinuria (> 1 g/24 h for at least 3 months) screened for participation in the Ramipril Efficacy in Nephrology (REIN) study. **Exclusion criteria** Overt heart failure, urinary tract infection **Population baseline characteristics:**		Urinary protein:creatinine ratio No. of patients 177 **Procedure** 177 patients provided spot morning urine samples at the clinic. Protein concentration was determined with a Synchron CX5 Beckman Analyzer. Creatinine concentration was measured by the Jaffe method on a Beckman Creatinine Analyzer II. The urine protein:creatinine	24-h urinary protein excretion No. of patients 177 **Procedure** 177 patients provided 24 hour urine collections the day before the scheduled clinic visit. Urine collection began immediately after completion of the first morning void and urine samples were then collected for 24 h, including the final void at the completion of the 24 h period.	Not applicable	Test correlation	Hoechst Marion Roussel supported the REIN trial
			N (entered REIN)	98					
			Mean protein:creatinine ratio (SD)	2.5 (1.7)					
			Mean urinary protein excretion (SD), g/24	2.8 (1.9)					
			% glomerular disease	20.4					
			% APKD or interstitial nephritis	3.1					
			% other/unknown cause CKD	76.5					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Mean age (SD), years	51.5 (14.1)	ratio was obtained by dividing the urinary protein concentration by the urine creatinine concentration.				
			% men	80.6					
Effect size **Test Correlation** In 177 patients, the correlation between spot morning urine protein:creatinine ratio and 24 h urinary protein excretion rates was highly significant (p=0.0001). Log-log transformation of the data showed a high correlation between spot morning urine protein:creatinine ratio and 24 h urinary protein excretion rate (r=0.932, p < 0.0001). The slope of the regression line (m=0.948) was almost identical to the line of unity (m=1), therefore protein:creatinine ratio is an excellent estimate of 24 h urinary protein excretion.									

Table 269: Ref ID: 590 [Marshall et al, 1986]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Marshall SM, Alberti KGMM. Screening for early diabetic nephropathy. Annals of Clinical Biochemistry. 1986; 23(2):195-197.	Study type Cross-sectional Diagnostic test II + No. centres Not stated; Newcastle upon Tyne, UK	Total N = 129 No. ITT= 129	**Inclusion criteria** Diabetic patients with urine negative to Albustix (proteinuria). **Exclusion criteria** Not stated. **Population baseline characteristics:** Very little detail provided.		First morning urinary albumin:creatinine ratio No. of patients 129 Procedure Patients provided first morning urine samples which were frozen until assayed. Urinary albumin was measured bysensitive raioimmunoassay and creatinine was measured by a modified Jaffe method on a Beckman Astra multichannel	Timed overnight urinary albumin excretion No. of patients 129 Procedure Timed overnight urine collections were collected and frozen until assayed. Albumin excretion rate was calculated from the volume and duration of the urine sample.	Not applicable	Sensitivity Specificity	Northern Counties Kidney Research Fund and Novo Laboratories Limited.
			N total	129					
			N Insulin dependent diabetics	67					
			N Insulin dependent diabetics	62					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					analyzer.				
Effect size									
Urine test to identify albumin excretion rate > 30 microgram/min			**Sensitivity (%)**			**Specificity (%)**			
Overnight albumin:creatinine ratio ≥ 3.5 mg/mmol			98			63			
Overnight albumin:creatinine ratio ≥ 4.5 mg/mmol			96			72			
An overnight albumin:creatinine ratio > 3.5 mg/mmol had a sensitivity and specificity (98% and 63%, respectively) of predicting an albumin excretion rate of > 30 microgram/min. Furthermore, by raising the cutoff to 4.5 mg/mmol for the albumin:creatinine ratio, the sensitivity decreased , while the specificity increased (96% and 72%, respectively). The authors favour the use of measuring the albumin:creatinine ratio in an early morning urine sample and using a cutoff of > 3.5 mg/mmol to predict and albumin excretion rate > 30 microgram/min. This was due to the better sensitivity at this cutoff value than at 4.5 mg/mmol. However, there are more false positives generated with a cut-off > 3.5 and this could put an extra burden on lab staff.									

Q.5.3.2 Call for Evidence: What is the equivalence between urinary albumin:creatinine ratios and 24 hour urinary protein excretion and urinary protein:creatinine ratio?

Table 270: Ref ID: 3996 [MacGregor et al. 2007]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
MacGregor MS, Traynor JP, O'Reilly DSJ et al. Assessing proteinuria in chronic kidney disease: protein-creatinine ratio versus albumin-creatinine ratio. 2007. Ref ID: 3996	Study type Retrospective analysis of laboratory database Diagnostic Test 1b + Scotland Aim: To compare ACR and PCR from same urine sample	N = 6761	**Inclusion criteria**: Adults > 18 years old with CKD attending a hospital kidney clinic. **Exclusion criteria:** data on urine samples prior to Nov. 1999, children < 18 years old **Population baseline characteristics:**		Urinary protein:creatinine ratio (PCR) Urinary albumin:creatinine ratio (ACR) N= 6761 **Procedure** Database (Proton, UK) searched for patients who had an ACR and PCR measured on the same date. The most recent paired results were used. Urine albumin was assayed with an anti-human albumin antiserum immunoturbidometric assay. Urine total protein was assayed on the same analyser using pyrogallol red. Urine creatinine concentration was determined with reaction rate Jaffe.	24-h urinary protein excretion also ACR vs.PCR N= 6761	N/A	Test correlation AUC Sensitivity Specificity	Not stated
			N	6761					
			Median eGFR, ml/min/1.73 m^2	40					
			Mean age (SD), years	60 (17)					
			% men	50.7					
			% unknown cause	26.8					
Effect size									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Data missing to ensure confidentiality of unpublished results								

Table 271: Ref ID: 3995 [Atkins et al. 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Atkins RC, Briganti EM, Zimmet PZ et al. Association between albuminuria and proteinuria in the general population: the AusDiab Study. Nephrol Dial Transplant. 2003; 18(10):2170-2174. Ref ID: 3995	Study type Cross-sectional study Diagnostic test II + (no gold standard, unable to assess blinding) Australia Aim: To compare ACR and PCR from same urine sample	N = 10596	Inclusion criteria: a representative sample of non-institutionalised people 25 years of age or older in Australia was drawn from 42 randomly selected urban and non-urban areas. Exclusion criteria: not stated Population baseline characteristics: Albuminuria was seen in 6.8% of the sample. Proteinuria was seen in 2.4% of the samples. Of people with proteinuria, 91% had albuminuria and 9% had a normal ACR. Of people with albuminuria, 32% had proteinuria and 68% had	Urinary albumin:creatinine ratio (ACR) N= 10596 Procedure: Participants completed a health questionnaire, had a clinical exam, and laboratory tests to examine diabetes status, CV risk, and renal function. Random urine samples were analysed at a central laboratory and measured for urine albumin (rate nephrelometry, Beckman array, CV < 3.1%) and urine protein (pyrogallol red molybdate , Olympus AU600 autoanalyser, CV < 4.1%). Urine creatinine was measured (modified	Urinary protein:creatinine ratio (PCR) N= 10596	N/A	Test correlation Sensitivity Specificity PPV NPV	Commonwealth Dept. of Health and Aged Care, Australian State Govts., Eli Lilly, Roche, Merck, Knoll, Smithkline Beecham, Pharmacia and Upjohn, BioRad, Quantas

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			a normal PCR. People with proteinuria or albuminuria were significantly older, had higher prevalences of diabetes and hypertension compared with those with neither proteinuria nor albuminuria.	kinetic Jaffe, Olympus AU600 autoanalyser, CV < 1.1%). Proteinuria was defined as protein:creatinine ratio ≥ 0.20 mg/mg or a protein excretion rate ≥ 250 mg/day. Albuminuria was defined as a urine albumin:creatinine ratio ≥ 30mg/g.				

Effect size

Test Correlation

Albuminuria was significantly correlated with proteinuria [log ACR versus log PCR: beta = 1.21 (95% CI 1.18 to 1.26), p <0.001, R2 = 72.1%, N samples =10596]. The graph showed convergence to the line of unity between ACR and PCR with increasing PCR, suggesting increased proportion of albumin at higher levels of total protein excretion. However, there was scatter of ACR (below the line of unity) at lower levels of PCR.

The ratio of urine albumin: total protein significantly increased with increasing degrees of proteinuria from 0.21 for those with PCR 0-0.20 mg/mg up to 0.73 for people with PCR > 0.80 mg/mg (p < 0.001).

The correlation between albuminuria and proteinuria was significantly greater in people > 60 years compared with people < 60 years; diabetics versus non-diabeteics; hypertensives vs.non-hypertensives, BMI > 30 vs.BMI < 30 and GFR < 60 versus GFR > 60.

Sensitivity and specificity

To detect proteinuria (a PCR ≥ 0.20 mg/mg), albuminuria (ACR ≥ 30 mg/g) had a sensitivity of 91.7% (95% CI 87.7 to 94.5%) and a specificity of 95.3% (95% CI 94.9 to 95.7%).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Positive and Negative Predictive Values: To detect proteinuria (a PCR ≥ 0.20 mg/mg), albuminuria (ACR ≥ 30 mg/g) had a PPV of 32.4% (95% CI 29.0 to 35.8%) and a NPV of 99.8% (95% CI 99.7 to 99.9%). Authors conclude that testing for albuminuria rather than proteinuria is supported. However, among people with known renal disease, total protein measures may provide better diagnostic/prognostic information (as among people with proteinuria, 9% tested negative for albuminuria).								

Table 272: Ref ID: 3988 [Ballantyne et al. 1993]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ballantyne FC, Gibbons J, O'Reilly DS. Urine albumin should replace total protein for the assessment of glomerular proteinuria. Ann Clin Biochem. 1993; 30 (Pt 1):101-103. Ref ID: 3988	Diagnostic Study II + 1 centre, UK Aim: To compare albumin to protein from the same 24-h urine sample	N = 235	**Inclusion criteria:** all 24-h urine samples referred to Institute of Biochemistry, Royal Infirmary, Glasgow, for urinary protein analysis. **Exclusion criteria:** not stated **Population**	urinary albumin (mg/l) in a 24-h urine sample N= 235 **Procedure** 24-h urine samples were assayed for protein with salicylsulphonic acid precipitation (to estimate the dilution factor for quantitative protein or albumin measurements). Urine albumin concentration (immunoturbidometric assay using human albumin antiserum/PEG, Encore centrifugal	urinary total protein in a 24-h urine sample (mg/l) N= 235	N/A	Test correlation	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			baseline characteristics: most samples came from a specialist renal unit	analyser) and urine total protein (Ponceau S, trichloroacetic acid precipitation, NaOH resolubilisation, read on a spectrophotometer at A560 nm) were assayed from each urine sample.				

Effect size

Within-run CV for total protein assay (N=10) was 3.0% at 0.22g/l and 2.4% at 0.5 g/l. Between day CV for total protein was 6.2% at 0.24 g/l and 2.8% at 0.66 g/l.

Within-run CV for albumin assay (N=18) was 3.4% at 10 mg/l and 2.4% at 75 mg/l. Between day CV for albumin was 5.1% at 17 mg/l and 5.1% at 103 mg/l.

N=235 urine samples screened positive for protein with salicylsulphonic acid.

Test Correlation

Albumin was plotted against total protein (log-log transformed) and the regression equation was albumin = 0.537 (total protein) - 9.472. The coefficient of correlation was high ($r=0.924$, $p<0.001$), indicating good agreement between total protein and albumin.

Albumin was also estimated in urines which tested negative for protein by salicylsulphonic acid precipitation. In all these samples, albumin concentration was < 100 mg/l and in most cases it was < 20 mg/l.

Authors conclude that there is good agreement between total protein and albumin overall and suggest replacing total protein measurements with albumin. measurements.

Note: no indication of blinding. Little description of the source of the urine samples.

Table 273: Ref ID: 7 [Newman et al. 1995]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Newman DJ, Thakkar H, Medcalf EA et al. Use of urine albumin measurement as a replacement for total protein. Clin Nephrol. 1995; 43(2):104-109. Ref ID: 7	Diagnostic Study II + 1 centre, UK Aim: To compare albumin to protein from the same 24-h urine sample	N = 167	**Inclusion criteria**: all 24-h urine samples referred to Dept. of Clinical Biochemistry for urinary protein analysis over a 4 month period. **Exclusion criteria:** not stated **Population baseline characteristics:** Source of urine sample: 45% renal transplant recipients, 14% obstetrics, 23% general medicine, 18% general renal investigations	24-h urinary albumin excretion (AER) N= 167 **Procedure** 24-h urine samples were centrifuged, and assessed with Albustix reagent strip to estimate the amount of dilution required to assay albumin and protein. Urine albumin concentration (latex particle enhanced immunoturbidometric assay, Monarch 2000 centrifugal analyser) and urine total protein (biuret, following trichloroacetic acid) and creatinine (direct Jaffe) were assayed from each urine sample.	24-h urinary total protein excretion (TPER) N= 167	N/A	Test correlation	Du Pont de Nemours International SA, Geneva
Effect size Albustix gave no false negative results, but several elevated results when compared with urine albumin or total protein. In samples with total protein excretion < 250 mg/24-h (N=73), 46 (63%) of the samples had a urine albumin excretion > 25 mg/24-h (the upper reference limit obtained from healthy subjects)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Test Correlation For all samples (N=167, range 0-16800 mg/l total protein), albumin excretion rate (AER) was plotted against total protein excretion rate (TPER) and regression analysis gave the equation AER = TPER (0.71) -118. This indicated that albumin formed 71% of the total protein (in the range 0-17000 mg/l total protein). The coefficient of correlation (r=0.93) was high indicating good agreement between AER and TPER, although most data points fell below the line of identity, showing that AER was less at a given TPER. For samples with total protein in the range 0-3000 mg/l (N=116), comparison of AER with TPER gave a regression equation of AER = TPER (0.51) + 7.5. The correlation coefficient (r=0.68) was low indicating poor agreement between AER and TPER in this range (0-3000 mg/l total protein). Most data points fell below the line of identity, showing that AER was less at a given TPER. Authors conclude that there is good agreement between AER and TPER overall and suggest replacing total protein measurements with albumin measurements. **Note:** no indication of blinding. Method of total protein determination not automated and could be more precise.								

Q.5.4 Managing isolated invisible haematuria (2014 guideline - chapter 5.5)

Table 274: Ref ID: 4080 [Yamagata et al. 2002]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yamagata K, Takahashi H, Tomida C et al. Prognosis of asymptomatic hematuria and/or	Prospective case series Evidenc	N isolated microscopic haematuria = 412	**Inclusion:** Japanese men with confirmed abnormal urinary findings (+1 result on a reagent strip urinalysis for haematuria and > 5 RBC/hpf by microscopy)	Long-term follow-up of men with asymptomatic microscopic haematuria N=404	N/A	6.35 years (range 1.03 to 14.6 years)	Diminished urinary abnormalities(four consecutive negative reagent strip results for haematuria)	Disease Control Division, Ministry of Health and

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
proteinuria in men. High prevalence of IgA nephropathy among proteinuric patients found in mass screening. Nephron. 2002; 91(1):34-42. Ref ID: 4080	e level: 3 Japan	8/412 = 2% lost to follow-up	identified in a mass screening between 1983 and 1996 in Hitachi, Japan **Exclusion criteria:** people with < 1 year follow-up **Population baseline characteristics:** not stated	**Procedure:** Medical history, BP, blood tests, USS of kidney and bladder were assessed at baseline. Urinalysis repeated at least twice/year, and symptoms and medical history recorded.			Deterioration of renal function (serum creatinine > 2.0 mg/dl) Development of proteinuria (chronic nephritic syndrome):	Welfare, Japan University of Tsukuba grant

Effect size:

41% (165/404) showed persistent haematuria

Diminished urinary abnormalities:

- Of 404 men with asymptomatic microscopic haematuria followed-up for > 1 year (mean follow-up 6.35 years), 46.5% had transient haematuria. The disappearance rate for haematuria was 34.1% (95% CI 29.4 to 39.7%).
- In men with asymptomatic microscopic haematuria, normotensive men were significantly more likely to see diminished urinary abnormalities compared with hypertensive men [rate ratio 4.393 (95% CI 1.616 to 11.944, p=0.0037]

Development of proteinuria (chronic nephritic syndrome):

- 38/404 (9%) men with asymptomatic haematuria developed proteinuria (chronic nephritic syndrome) during follow-up.

Deterioration of renal function (serum creatinine > 2.0 mg/dl)

- 0.7% of men with asymptomatic haematuria had a deterioration of renal function (creatinine > 2.0 mg/dl) during follow-up. The renal function deterioration rate for asymptomatic haematuria was 3.0% over 10 years.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• 17/404 with asymptomatic haematuria had renal biopsies and 13/17 were diagnosed as IgA nephropathy and 3/17 were diagnosed as mesangial proliferative glomerulonephritis **Note:** females excluded from analysis as their age distribution varied significantly from the general population.								

Q.5.5 Who should be tested for CKD (2014 guideline chapter 6.2)

Table 275: Borch-Johnsen et al. 1992

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Borch-Johnsen K, Norgaard K, Hommel E et al. Is diabetic nephropathy an inherited complication? Kidney Int. 1992; 41(4):719-722. Ref ID: 11	Case series Evidence level: 3 Denmark The study aimed to investigate the concordance rates for the presence or	N= 49 probands N=45 siblings of the probands	Nephropathy patients recruited from a specialised hospital diabetes care unit, non nephropathy patients recruited form hospital files in Denmark. **Inclusion criteria:** Diabetes onset before age of 40 years, unbroken record of insulin treatment, diabetes duration ≥ 10 years. **Exclusion criteria:** Sibling-pairs where the sibling had diabetes mellitus for < 5 years, no clinical or laboratory evidence of kidney or renal tract disease other than diabetic	Diabetic siblings of diabetic Probands with nephropathy (AER > 0.5 g/24-h) N= 21	Diabetic Siblings of diabetic probands without nephropathy (AER < 20 mg/24-h) N= 30	n/a	HbA1c, 24 hour urinary albumin excretion, serum creatinine.	Not mentioned

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
	absence of renal involvement in the diabetic siblings of insulin dependent diabetics		glomerulosclerosis. **Baseline characteristics:** There were significant differences between proband groups wrt: baseline HbA1c (p<0.02) which was lower in the group without nephropathy, more patients in the nephropathy group were on hypertensive medication (p<0.0001) and had a higher serum creatinine level (p<0.0001)					

Effect size

Incidence of nephropathy based on the nephropathy status of the proband

	Proband with clinical nephropathy	Proband without clinical nephropathy	p
Median AER (mg/24 hr)	79 (8-558)	14 (3-400)	<0.03
Sibling nephropathy	33% (7/21)	10% (3/30)	0.035
Sibling incipient or overt nephropathy (Urinary albumin excretion >100 mg/24 hrs)	43% (9/21)	13% (4/30)	0.017
Odds ratio	4.9 (1.3; 19.1)		

Diabetic siblings of people with diabetic nephropathy have a significantly increased risk of incipient or overt nephropathy compared to diabetic siblings of people without nephropathy [OR 4.9 (95% CI 1.3 to 19.1)].

Within the individual sib-pair, there was a significant positive correlation between the glycosylated haemoglobin A1c value of proband and sibling (r=0.47; p<0.001)

Table 276: Chadban et al. 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Chadban SJ, Briganti EM, Kerr PG et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. Journal of the American Society of Nephrology. 2003; 14(7:Suppl 2):Suppl-8. Ref ID: 3869	Cross-sectional population study AusDiab Australian population study Evidence Level: 3	N=11247	**Inclusion criteria:** a representative sample of non-institutionalised people 25 years of age or older in Australia was drawn from 42 randomly selected urban and non-urban areas. **Exclusion criteria:** not stated **Baseline Characteristics:** 97% Caucasian, 5.7% Asian, 0.8% Aboriginal and Torres Strait Islanders	Prevalence of proteinuria, hematuria or GFR < 60 ml/min/1.73m^2 In Australia. Procedure: Participants completed a health questionnaire, had a clinical exam, and laboratory tests to examine diabetes status, CV risk, and renal function. Serum creatinine was measured in all participants (Jaffe) and creatinine clearance was calculated with the Cockcroft-Gault equation. Impaired renal function was defined as GFR < 60 ml/min/1.73m^2. Protein:creatinine ratio (Jaffe method and pyrogallol red molybdate) from a morning spot urine sample was determined.	Effect of increasing age, effect of gender, effect of hypertension, diabetes	N/A	Proteinuria Hematuria GFR < 60 ml/min/1.73m^2	Commonwealth Dept. of Health and Aged Care, Australian State Govts., Eli Lilly, Roche, Merck, Knoll, Smithkline Beecham, Pharmacia and Upjohn, BioRad, Quantas

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
				Proteinuria was defined as protein:creatinine ratio ≥ 0.20 mg/mg. Hematuria was defined as positive if reagent strip testing of morning urine sample was ≥ +1 and microscopy showed ≥ 10000 RBC/microL.				

Effect size:

OR adjusted for age, sex, diabetes, hypertension

In this Australian sample (N=11247), the prevalence of proteinuria (protein:creatinine ratio ≥ 0.20 mg/mg) was 2.4%. The prevalence of hematuria (reagent strip ≥ +1 and microscopy ≥ 10000 RBC/microL) was 4.6%. The prevalence of renal impairment (GFR < 60 ml/min/1.73m^2) was 11.2%.

Using proteinuria and hematuria data, the prevalence of Stage 1 CKD in Australia was 0.9%, Stage 2 was 2.0%, Stage 3 was 10.9%, Stage 4 was 0.3%, Stage 5 was 0.003%.

Age as a risk factor for Renal Impairment (GFR < 60 ml/min/1.73m^2)

54% of people ≥ 65 years old had GFR < 60 ml/min/1.73m^2 compared with 2.5% of subjects 45-64 years old. People ≥ 65 years old had a significantly increased risk of renal impairment (GFR < 60 ml/min/1.73m^2) compared with people < 65 years old [adjusted OR 101.5 (95% CI 61.4 to 162.9), p<0.001]

Gender as a risk factor for Renal Impairment (GFR < 60 ml/min/1.73m^2)

Females had a significantly higher risk of renal impairment than males [adjusted OR 1.3 (95% CI 1.0 to 1.7), p=0.012]

Diabetes as a risk factor for Renal Impairment (GFR < 60 ml/min/1.73m^2)

People with diabetes had NS risk of renal impairment than people without diabetes [adjusted OR 0.9 (95% CI 0.7 to 1.1), p=0.308]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hypertension as a risk factor for Renal Impairment (GFR < 60 ml/min/1.73m^2) People with hypertension had a significantly higher risk of renal impairment compared with normotensive people [adjusted OR 1.4 (95% CI 1.2 to 1.6), p<0.001] **Age as a risk factor for Proteinuria (protein:creatinine ratio ≥ 0.20 mg/mg) :** The prevalence of proteinuria increased with increasing age. People ≥ 65 years old had a significantly increased risk of proteinuria than people < 65 years old [adjusted OR 2.5 (95% CI 1.9 to 3.2), p<0.000] **Gender as a risk factor for Proteinuria (protein:creatinine ratio ≥ 0.20 mg/mg)** Men and women had similar prevalences of proteinuria. **Diabetes as a risk factor for Proteinuria (protein:creatinine ratio ≥ 0.20 mg/mg)** People with diabetes had a significantly higher risk of proteinuria than people without diabetes [adjusted OR 2.5 (95% CI 1.8 to 3.5), p<0.001] **Hypertension as a risk factor for Proteinuria (protein:creatinine ratio ≥ 0.20 mg/mg)** People with hypertension had a significantly greater risk of proteinuria than people with normotension [adjusted OR 3.1 (95% CI 2.3 to 4.1), p<0.001] **Age as a risk factor for Hematuria (reagent strip testing of morning urine sample was ≥ +1 and microscopy showed ≥ 10000 RBC/microL.)** Hematuria increased with increasing age (p<0.001 for trend). **Gender as a risk factor for Hematuria (reagent strip testing of morning urine sample was ≥ +1 and microscopy showed ≥ 10000 RBC/microL.)** Females had a significantly higher risk of hematuria than males [adjusted OR 3.9 (95% CI 2.8 to 5.3), p<0.001] **Diabetes as a risk factor for Hematuria (reagent strip testing of morning urine sample was ≥ +1 and microscopy showed ≥ 10000 RBC/microL.)** People with diabetes had a significantly decreased risk of hematuria than people without diabetes [adjusted OR 0.5 (95% CI 0.3 to 0.8), p=0.008]								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hypertension as a risk factor for Hematuria (reagent strip testing of morning urine sample was ≥ +1 and microscopy showed ≥ 10000 RBC/microL.) There was NS difference in the prevalence of hematuria in hypertensive or normotensive people (5.0% vs.4.5%, p=0.44) **Note:** Limitations –Cross-sectional analysis.								

Table 277: Coresh et al., 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Coresh J, Astor BC, Greene T et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003; 41(1):1-12. Ref ID: 3872	Cross-sectional population study NHANES III US population study Evidence Level: 3	N=15600	**Inclusion criteria:** a general health survey was conducted in USA in 1988-1994 of non-institutionalised adults 20 years or older. Random selection using a stratified cluster method. **Exclusion criteria:** CKD stage 5 **Baseline Characteristics:** not applicable	Prevalence of CKD in USA **Procedure:** Non-Hispanic blacks, elderly, and American Mexicans were deliberately over-sampled. Participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the MDRD equation re-calibrated to the MDRD laboratory. CKD was defined according to GFR and staged according to KDOQI. Albumin:creatinine ratio determination (by Jaffe method and solid phase fluorescent immunoassay assay of albumin) from a random urine sample was determined. A subset of participants (N=1241) was used to estimate the persistence of microalbuminuria within 2 months of the first examination.	Effect of increasing age, effect of gender, effect of hypertension, diabetes, ethnicity	N/A	CKD defined by KDOQI stratification of GFR	National Institutes of Health, National Kidney Foundation, General Research Center
Effect size								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

OR adjusted for age, sex, diabetes, hypertension, hypertension medication.

In this American sample (N=15600), the prevalence of mild CKD (GFR 60-89 ml/min/1.73 m^2) was 31.2%. The prevalence of moderate CKD (GFR 30-59 ml/min/1.73 m^2) was 4.3% and the prevalence of severe CKD (GFR 15-29 ml/min/1.73 m^2) was 0.2%.

Using microalbuminuria data, the prevalence of Stage 1 CKD in the USA was 3.3%, Stage 2 was 3.0%, Stage 3 was 4.3%, Stage 4 was 0.2%, and Stage 5 was 0.2%. The overall prevalence of CKD in USA was 11%.

Age as a risk factor for CKD:

The prevalence of CKD increased with increasing age. 48% of people > 70 years of age (N=2965) had mild CKD (GFR 60-89 ml/min/1.73m2) and 25% had moderate to severe CKD (GFR < 60 ml/min/1.73m2).

Gender as a risk factor for CKD:

The prevalence of decreased kidney function was higher in women than men, but this difference disappeared after adjustment for age.

Hypertension as a risk factor for CKD:

People with hypertension (N=4893) had a greater risk of CKD than people without hypertension (N=14372). Among hypertensive people, people taking antihypertensive medication had the highest prevalence of decreased kidney function (this may reflect the severity or duration of hypertension in this subgroup). For example, 17.5% of hypertensive people taking antihypertensive agents (N=2553) and 7.9% of hypertensive people not taking medication (2340) had moderate CKD (GFR 30-59 ml/min/1.73m2) compared to 1.5% of non-hypertensive people (N=10707).

Diabetes as a risk factor for CKD:

People with diabetes (N=1211) had a higher prevalence of decreased kidney function than people without diabetes (N=14372). 40% of people with diabetes had mild CKD (GFR 60-89 ml/min/1.73m2) whereas 31% of people without diabetes had mild CKD (GFR 60-89 ml/min/1.73m2). 14% of people with diabetes had moderate CKD (GFR 30-59 ml/min/1.73m2) whereas 3.7% of people without diabetes had moderate CKD (GFR 30-59 ml/min/1.73m2).

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Ethnicity as a risk factor for CKD Non-Hispanic black people (N=4163) were significantly less likely to have mild CKD (GFR 60-89 ml/min/1.73m2) compared to non-Hispanic white people (N=6635) [adjusted OR 0.37 (95% CI (0.32 to 0.43)]. Non-Hispanic black people (N=4163) were significantly less likely to have moderate CKD (GFR 30-59 ml/min/1.73m2) compared to non-Hispanic white people (N=6635) [adjusted OR 0.56 (95% CI (0.44 to 0.71)]. There was NS difference in prevalence of severe CKD (GFR 15-29 ml/min/1.73m2) in Non-Hispanic black or white people [adjusted OR 1.10 (95% CI (0.51 to 2.37)]. **Note:** Limitations –Cross-sectional analysis.								

Table 278: Coresh et. al 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298(17):2038-2047. Ref ID: 22	Cross-sectional population study NHANES US population study Evidence Level: 3	NHANES 1988-1994 N= 15488 NHANES 1999-2004 N=13233	**Inclusion criteria:** a general health survey was conducted in USA in 1988-1994 and again in 1999-2004 of non-institutionalised adults 20 years or older. Random selection using a stratified cluster method. **Exclusion criteria:** Stage 5 CKD, people with missing creatinine values Baseline Characteristics: not applicable	Prevalence of CKD in USA ascertained by NHANES 1999-2004 **Procedure:** Non-Hispanic blacks, elderly, and American Mexicans were deliberately over-sampled. Participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the simplified MDRD equation re-calibrated to the MDRD laboratory. CKD was defined according to GFR and staged according to KDOQI. Albumin:creatinine ratio determination (by Jaffe method and solid phase fluorescent immunoassay assay of albumin) from a random urine sample was	Prevalence of CKD in USA ascertained by NHANES 1988-1994	N/A	CKD defined by KDOQI stratificatio n of GFR	National Institute of Diabetes, and Digestive and Kidney Diseases

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
				determined. A subset of participants from NHANES 1988-1994 (N=1241) was used to estimate the persistence of microalbuminuria within 2 months of the first examination.				

Effect size

This paper compares prevalence of CKD in the USA determined in NHANES 1988-1994 compared with NHANES 1999-2004.

The prevalence of diabetes, hypertension, high BMI increased from NHANES 1988-1994 to NHANES 1999-2004.

Mean ACR also increased from NHANES 1988-1994 (mean ACR 25.4 mg/g; N=14319) to NHANES 1999-2004 (mean ACR 28.6 mg/g; N=12216).

Prevalence of CKD significantly increased in the USA from NHANES 1988-1994 to NHANES 1999-2004:

	NHANES 1988-1994 (N=15488)		**NHANES 1999-2004 (N=13233)**		
	N	**Prevalence (%)**	**N**	**Prevalence (%)**	**P-value (between 2 NHANES studies)**
GFR ≥ 90 ml/min/1.73 m^2	8600	51.9	5891	40.7	<0.001
GFR 60-89 ml/min/1.73 m^2	5751	42.4	5946	51.2	<0.001
GFR 30-59 ml/min/1.73 m^2	1088	5.4	1316	7.7	<0.001
GFR 15-29 ml/min/1.73 m^2	49	0.21	80	0.35	0.02
Normal ACR (< 30 mg/g)	12655	91.8	10636	90.5	0.01
Microalbuminuria (ACR 30-299 mg/g)	1353	7.1	1315	8.2	0.01
Macroalbuminuria (ACR ≥ 300 mg/g)	311	1.1	265	1.3	0.37 NS

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Stage 1 CKD *	Not stated	1.71	Not stated	1.78		NS		
Stage 2 CKD *	Not stated	2.70	Not stated	3.24		Stated as significant, no p given		
Stage 3 CKD	Not stated	5.42	Not stated	7.69		Stated as significant, no p given		
Stage 4 CKD	Not stated	0.21	Not stated	0.35		Stated as significant, no p given		
Stage 5 CKD	N/A	N/A	N/A	N/A		N/A		
Total CKD	Not stated	10.03	Not stated	13.07		Stated as significant, no p given		

* based on persistent albuminuria

The prevalence of CKD increased with increasing age and this was a similar trend in the two NHANES studies. Approx 47% of people > 70 years old had CKD (NHANES 1999-2004) compared with 37% of people > 70 years old (NHANES 1988-1994)

The prevalence of GFR < 60 ml/min/1.73 m^2 was significantly higher in the NHANES 1999-2004 study compared with the NHANES 1988-1994 study even after adjustment for age, race, sex, diabetes, hypertension, BMI [adjusted OR 1.43 (95% CI 1.24 to 1.63), p<0.001].

Age, race, sex, diabetes, hypertension, and BMI explained the entire increase in the prevalence of albuminuria in NHANES 1999-2004 compared with NHANES 1988-1994.

Note: Limitations –Cross-sectional analysis; GFR measured from creatinine, not iothalamate or other gold standard, MDRD predictive equation has greater imprecision and bias at greater GFR (could misclassify mild kidney disease), persistence of albuminuria calculated from small data set, and assumed to be the same across the 2 surveys

Table 279: Drey et al., 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Drey N, Roderick P, Mullee M et al. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. American Journal of Kidney Diseases. 2003; 42(4):677-684. Ref ID: 695	Cross-sectional population study UK population study Evidence Level: 3	N=404541	**Inclusion criteria:** new cases of CKD in Southampton and South-west Hampshire health authority identified in 1992-1994 from chemical pathology databases at Southampton University hospitals NHS. CKD was defined as a serum creatinine value > 1.7 mg/dl or >150 micromol/l persisting for six months or more. **Exclusion criteria:** cases before 1992, serum creatinine decreases to < 1.7 mg/dl within 6 months, electoral wards that referred < 80% of their patients for inpatient treatment in S&SWH HA, cases not resident in Southampton and South-west Hampshire health authority **Baseline Characteristics:** a mostly Caucasian UK population	Incidence of CKD **Procedure:** a dataset of demographic, laboratory, diagnostic and prescription variables were extracted from patient records. A deprivation score was assigned to each patient according to area of residence (postcode).	Incidence of CKD with increasing age, effect of gender, effect of socioeconomic deprivation	N/A	CKD	National Health Service South West Regional Health Authority

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

There were 4228 new cases of kidney disease identified in 1992-1994.

The incidence of CKD (defined as a serum creatinine value > 1.7 mg/dl or >150 micromol/l persisting for six months or more) in the study population was 1701 per million population (95% CI 1613 to 1793 pmp). For people < 80 years old, the incidence was 1071 pmp (95% CI 1001 to 1147).

Age as a risk factor for CKD:

The incidence of CKD (serum creatinine value > 1.7 mg/dl or >150 micromol/l) increased with increasing age. 74% of CKD cases (792/1076 definite CKD cases) were identified in people ≥ 70 years old.

Gender as a risk factor for CKD:

Overall, 60% of new CKD cases were found in men (650/1076 definite CKD cases). The man:woman rate ratio was 1.6 (95% CI 1.4 to 1.8). The preponderance of men with CKD was significant in all ages > 40 years of age.

Socioeconomic deprivation as a risk factor for CKD:

People who were least deprived (Townsend score =1) had a significantly lower risk of CKD compared to the overall population [directly standardised rate ratio 0.80 (95% CI 0.69 to 0.93)]

People who were most deprived (Townsend score =5) had a significantly higher risk of CKD compared to the overall population [directly standardised rate ratio 1.17 (95% CI 1.02 to 1.33)]

Note: Limitations – Relies on blood test alone to identify CKD and 1.7 mg/dl as the cut-off is arbitrary and not sensitive to reduced renal function. MDRD GFR would have perhaps been a better indicator of renal function. Cross-sectional analysis by retrospectively reviewing medical records. Although a UK study, it was a predominantly Caucasian sample -caution in applying to areas of high ethnic diversity.

Table 280: Elsayed et al., 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Elsayed EF, Tighiouart H, Griffith J et al. Cardiovascular Disease and Subsequent Kidney Disease. Archives of Internal Medicine. 2007; 167(11):1130-1136. Ref ID: 3940	case series Evidence level: 3 USA	N total = 13826 N Subjects with CVD = 1787 N Subjects without CVD = 12039	**Inclusion:** patient data pooled from Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS). ARIC: people 45-64 years old recruited between 1987 and 1989 from 4 communities. CHS: subjects ≥ 65 years old recruited between 1989 and 1990. **Exclusion criteria:** participants with missing data (including baseline or final creatinine measurements), people with baseline GFR < 15 ml/min/1.73 m^2 Population baseline	Subjects with CVD N = 1787 **Procedure:** Baseline serum creatinine measured and calibrated to Third NHANES values. MDRD equation used to estimate GFR. Baseline cardiovascular disease (CVD) defined by stroke, angina, claudication, TIA, coronary angioplasty or bypass, or recognised or silent MI.	Subjects without CVD N = 12039 **Procedure:** As for intervention	Mean 9.3 years. 22% failed to provide last serum creatinine; these people were more likely to have CVD at baseline and had higher CVD risk factors. Authors suggest this exclusion would bias towards null hypothesis.	Kidney function decline (serum creatinine increase of at least 0.4 mg/dl between first and last visit) Kidney function decline (GFR decrease of at least 15 ml/min/1.73 m^2 between first and last visit) Development of CKD (serum creatinine increase of at least 0.4 mg/dl from baseline level of < 1.4 mg/dl in men and < 1.2 mg/dl in women)	NIH, Amgen, National Heart, Lung, and Blood Institute

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			characteristics: Mean age 57.6 years. People with baseline CVD were significantly older (60 vs.57 years), had higher prevalence of diabetes and hypertension, and had lower baseline GFR (86 vs.90 ml/min/1.73 m^2) compared to people without CVD at baseline.				Development of CKD (GFR decrease of 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2)	

Effect size:

Odds ratios (OR) adjusted for age, sex, race, education, study origin, diabetes, smoking, alcohol use, hypertension history, BMI, SBP, hematocrit, albumin level, HDL cholesterol, total cholesterol, baseline serum creatinine, baseline eGFR.

Effect of Cardiovascular disease on Kidney Function decline (serum creatinine increase of at least 0.4 mg/dl between first and last visit)

After a mean follow-up of 9.3 years, 128 of 1787 (7.2%) people with baseline cardiovascular disease had a decline in kidney function (serum creatinine increase of at least 0.4 mg/dl) compared with 392 of 12039 (3.3%) people without baseline CVD (p<0.001). People with decline in renal function were significantly older, more likely to have hypertension and diabetes, more likely to be African American, and had significantly higher baseline serum creatinine levels than those who did not experience renal function decline.

People with baseline cardiovascular disease (N=1787) had a significantly increased risk of a decline in renal function (serum creatinine increase of at least 0.4 mg/dl) compared with people without CVD at baseline (N=12039) [adjusted OR 1.70 (95% CI 1.36 to 2.13), p<0.001).

Effect of Cardiovascular disease on Kidney Function decline (GFR decrease of at least 15 ml/min/1.73 m^2 between first and last visit)

After a mean follow-up of 9.3 years, 607 of 1787 (34.0%) people with baseline cardiovascular disease had a decline in kidney function (GFR decrease of at least 15

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

ml/min/1.73 m^2) compared with 3909 of 12039 (32.5%) people without baseline CVD (p=0.22).

People with baseline cardiovascular disease (N=1787) had a significantly increased risk of a decline in renal function (GFR decrease of at least 15 ml/min/1.73 m^2) compared with people without CVD at baseline (N=12039) [adjusted OR 1.28 (95% CI 1.13 to 1.46), p<0.001).

Effect of Cardiovascular disease on Development of CKD (serum creatinine increase of at least 0.4 mg/dl from baseline level of < 1.4 mg/dl in men and < 1.2 mg/dl in women)

People with baseline CVD and baseline serum creatinine < 1.4 mg/dl in men and < 1.2 mg/dl in women had a significantly increased risk of developing CKD (serum creatinine increase of at least 0.4 mg/dl)compared with people without CVD at baseline [adjusted OR 1.75 (95% CI 1.32 to 2.32), p<0.001).

Effect of Cardiovascular disease on Development of CKD (GFR decrease of at least 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2)

People with baseline CVD had an increased risk of developing CKD (GFR decrease of at least 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2) compared with people without baseline CVD [adjusted OR 1.54 (95% CI 1.26 to 1.89), p<0.001).

Sensitivity Analyses:

Similar increased risk when analysis was restricted to ARIC or CHS cohorts separately.

Exclusion of people with heart failure: association still remained significant [OR 1.72 (1.12 to 2.62)].

Baseline ACE inhibitors use evaluated: CVD still associated with kidney function decline [OR 1.82 (1.20 to 2.76)] and ACE inhibitors use was protective [OR 0.30 (0.10 to 0.87)].

CVD defined as only MI or cardiac procedure: CVD still associated with decline in kidney function [OR 1.93 (1.45 to 2.59)].

Limitations: no baseline proteinuria data, ARIC study lacked data on ACE inhibitors use.

Table 281: Freedman et al., 1997

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Freedman BI, Soucie JM, McClellan WM. Family history of end-stage renal disease among incident dialysis patients. Journal of the American Society of Nephrology. 1997; 8(12):1942-1945. Ref ID: 1382	case series Evidence level: 3 US study	N ESRD total = 4289 N ESRD No family history ESRD =3433 N ESRD with family history of ESRD= 856	**Inclusion criteria:** patients ≥ 20 years old with ESRD initiating RRT in dialysis units in North Carolina, South Carolina, and Georgia during 1994 **Exclusion criteria:** Mendelian cause of ESRD (polycystic kidney disease, Alport syndrome), urological conditions, surgical nephrectomy, ethnicities other than black or white **Baseline data:** mean age 58.4 years, 79% > 45 years old, 62% African American, 40% ESRD associated with diabetes, 39% associated with hypertension, 10%	Assessed effect of race and cause of ESRD on odds of having a family history of ESRD. Procedure: Participation of patients initiating RRT was voluntary. A family history of ESRD was considered present if an incident ESRD patient reported having either a first-degree (parent, child, sibling) or second-degree (grandparent, aunt, uncle, grandchild, or half-sibling) relative with ESRD. ESRD defined at dialysis, kidney transplant, or death from kidney disease before dialysis was started. A standardised data-collection instrument was used to collect data on presence of ESRD in first and second degree relatives, total number of siblings and children. Age, sex, race, weight, height of patients, primary cause of ESRD, co morbidities,	N/A	N/A	A family history of ESRD	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			associated with chronic glomerular disease, 11% "other" cause.	laboratory results at dialysis initiation obtained from Centres for Medicare and Medicaid Services Form 2728.				

Effect size:

Odds ratios (OR) adjusted for race, gender, age, state of residence, cause of ESRD, education

856/4289 (20%) people with ESRD reported having a family history of ESRD.

In crude analysis, hypertension, diabetes, glomerulonephritis, black ethnicity were all associated with increased odds of a family history of ESRD.

Effect of Race on odds of a family history of ESRD

African American men with ESRD (N=1172) were significantly more likely to report a family history of ESRD than white men with ESRD (N=915) [adjusted OR 1.8 (95% CI 1.4 to 2.3)] Similar risk for African American women compared with white men.

Effect of Hypertension on odds of a family history of ESRD

People with ESRD and a history of hypertension (N=1658) were significantly more likely to report a family history of ESRD than people with ESRD due to "other" causes (N=461) [adjusted OR 1.5 (95% CI 1.1 to 2.1)]

Effect of diabetes on odds of a family history of ESRD

People with ESRD and a history of diabetes (N=1720) were significantly more likely to report a family history of ESRD than people with ESRD due to "other" causes (N=461) [adjusted OR 1.9 (95% CI 1.4 to 2.6)]

Effect of glomerulonephritis on odds of a family history of ESRD

People with ESRD due to glomerulonephritis (N=450) were significantly more likely to report a family history of ESRD than people with ESRD due to "other" causes (N=461) [adjusted OR 2.1 (95% CI 1.5 to 3.0)]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: authors concede that in the African American index cases, 88% of the family history data was correct (no comparable data from Caucasian index), meaning that the family history of ESRD data could have been overestimated, although authors doubt this overestimation could completely account for the increased odds of a family history of ESRD in African Americans compared with Caucasians.								

Table 282: Gelber et al. 2005

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Gelber RP, Kurth T, Kausz AT et al. Association between body mass index and CKD in apparently healthy men. American Journal of Kidney Diseases. 2005; 46(5):871-880. Ref ID: 349	Prospective cohort study Physician's Health Study USA Evidence level: 2 +	N total = 11104 N BMI< 22.7 kg/m^2=2202 N BMI 22.7-23.7 kg/m^2=2277 N BMI 23.8-25.0 kg/m^2=2155 N BMI 25.1-26.6 kg/m^2=2250 N BMI > 26.6 kg/m^2=2220	**Inclusion criteria:** Healthy male physicians participating in the Physicians' Health Study (PHS), a completed RCT of aspirin or beta carotene in the primary prevention of CVD and cancer. **Exclusion criteria:** History of CVD, cancer, current liver disease or renal failure/insufficiency, major illness **Baseline characteristics:** Overweight (BMI 25-29.9 kg/m^2) and obese (BMI > 30 kg/m^2) males were more likely to have hypertension, diabetes, or CVD, more likely to smoke, less physically active, and drank less alcohol than males with BMI < 25 kg/m^2.	Males with BMI 22.7-23.7 kg/m^2=2277 BMI 23.8-25.0 kg/m^2=2155 BMI 25.1-26.6 kg/m^2=2250 BMI > 26.6 kg/m^2=2220 **Procedure:** The follow-up blood sample assayed for creatinine (Jaffe method) and GFR calculated with MDRD equation. BMI was calculated from self-reported weight and height. Baseline and follow-up information on demographics, medical history, height, weight, health behaviour, medication use, newly diagnosed conditions assessed from annual self-reported questionnaires	Males with BMI < 22.7 kg/m^2=2202	14 years	CKD (defined as GFR < 60 ml/min/1.73m^2) at 14-year follow-up	National Cancer Institute and National Heart, Lung, and Blood Institute

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size Odds ratios (OR) adjusted for baseline age, smoking, alcohol intake, exercise, history of MI before age 60, diabetes, hypertension, elevated cholesterol, CVD during follow-up. Of 11104 males, 1377 (12%) had a GFR < 60 ml/min/1.73m^2 and 4.4% had a creatinine level > 1.5 mg/dl after 14 years follow-up. **BMI effects on risk of CKD** The risk of developing CKD (GFR < 60 ml/min/1.73m^2) increased with increasing BMI (p trend = 0.007) Compared to men with BMI < 22.7 kg/m^2 (N=2202), men with BMI > 26.6 kg/m^2 (N=2220) had a significantly increased risk of developing CKD [adjusted OR 1.26 (95% CI 1.03 to 1.54)] Compared to men with BMI < 22.7 kg/m^2 (N=2202), men with BMI 25.1-26.6 kg/m^2 (N=2250) had a significantly increased risk of developing CKD [adjusted OR 1.32 (95% CI 1.09 to 1.61)] There was NS risk of CKD for men with BMI 22.7-23.7 (N=2277) or BMI 23.8-25.0 (N=2155)compared to men with BMI < 22.7 kg/m^2 (N=2202) Each 1-unit increase in baseline BMI was associated with a 5% increase in CKD risk [OR 1.05 (95% CI 1.03 to 1.07)]. Compared to men who remained within ± 5% range of their baseline BMI (N=5670), men who had a > 10% increase in BMI (N=1669) had a significantly increased risk of CKD [OR 1.24 (95% CI 1.03 to 1.50)] **Assessment of bias:** data was self-reported, creatinine values were not available at baseline so they could not confirm that participants were free of renal disease at baseline, confounding from other variables not taken into account/unknown, a male, predominantly Caucasian sample.								

Table 283: Hallan et al. 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hallan SI, Coresh J, Astor BC et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006; 17(8):2275-2284. Ref ID: 3871	Cross-sectional population study Norway HUNT II population study Evidence Level: 3	N=65181	**Inclusion criteria:** a general health survey was conducted in Nord-Trondelag county, Norway in 1995-1997. Adults 20 years or older. **Exclusion criteria:** CKD stage 5, menstruating women or people with UTI a week before measurement of ACR, **Baseline Characteristics:** mean age 50.2 years, 10% were 70 years of age or older, 44% hypertensive, 3.4% diabetic, 11% taking antihypertensive agents, 33% smokers, 8% had previous MI, stroke, or angina pectoris,	Prevalence of CKD in Norway **Procedure:** participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the MDRD equation. CKD was defined according to GFR and staged according to KDOQI. A 5% random sample of the population submitted three consecutive morning urine samples for albumin:creatinine ratio determination (by Jaffe method and immunoturbidometric assay of albumin). People with 2 or 3 ACR determinations of 17-250 mg/g (men) or 25-355 mg/g (women) were classified as having persistent microalbuminuria. Macroalbuminuria was defined	Prevalence of CKD in USA Effect of increasing age, effect of gender, effect hypertension, diabetes	N/A	CKD	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
				as 1 or more ACR measurements higher than the microalbuminuric range.				

Effect size:

In this Norwegian population (N=65181), the prevalence of mild CKD (GFR 60-89 ml/min/1.73m^2) was 38.6%. The prevalence of moderate CKD (GFR 30-59 ml/min/1.73m^2) was 4.5% and the prevalence of severe CKD (GFR 15-29 ml/min/1.73m^2) was 0.2%.

Age as a risk factor for CKD:

The prevalence of CKD increased with increasing age. The prevalence of GFR < 60 ml/min/1.73m^2 was 50-100 times greater in people > 70 years old compared to people 20-39 years old.

Gender as a risk factor for CKD:

Women had a significantly higher risk of CKD than men [age-adjusted OR 1.5 (95% CI 1.4 to 1.6)].

Hypertension as a risk factor for CKD:

20% of hypertensive people had moderate CKD (GFR 30-59 ml/min/1.73m^2) compared to 2% of normotensive people. People with hypertension had a higher risk of CKD than people without hypertension [age-adjusted OR 1.5 (95% CI 1.3 to 1.6)].

Diabetes as a risk factor for CKD:

13.6% of diabetic people had moderate CKD (GFR 30-59 ml/min/1.73m^2) compared to 4% of non-diabetic people. People with diabetes had a significantly higher risk of CKD than people without diabetes [age-adjusted OR 1.5 (95% CI 1.3 to 1.7)].

Comparison between Norway and USA prevalence of CKD:

The Norwegian prevalence of Stages 1-4 CKD was 10.2% (95% CI 9.2 to 11.2) and the American prevalence was 11.7%.

However, progression to ESRD was much slower in Norwegians than in Americans. White Americans had a 2 times higher risk for ESRD compared to Norwegians

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
(mostly white). This difference may be due to higher rates of obesity in the American participants (adjusted for diabetes, hypertension, age). **Note:** Limitations –Cross-sectional analysis. Participants were volunteers, so may have selection bias (participation increased with increasing age) Although a European study, it was a predominantly Caucasian sample -caution in applying to areas of high ethnic diversity.								

Table 284: Hallan et al. 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hallan SI, Dahl K, Oien CM et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey.[see comment]. BMJ. 2006; 333(7577):1047. Ref ID: 4109	Cross-sectional population study Norway HUNT II population study Evidence Level: 3	N asked to participate =92939 N = 65604 participated 70.6% participation rate	**Inclusion criteria:** a general health survey was conducted in Nord-Trondelag county, Norway in 1995-1997. Adults 20 years or older. **Exclusion criteria:** CKD stage 5, menstruating women or people with UTI a week before measurement of ACR, **Baseline Characteristics:** median age 49 years, 11% taking antihypertensive agents, 3.0% diabetic, 27% smokers, 37% family history of hypertension or diabetes, 7.9% CVD, mean GFR 94.6 ml/min/1.73 m^2, 4.7% GFR < 60 ml/min/1.73 m^2	Different screening strategies for detection of CKD (Stage 3-5) were compared in Norway GFR 45-59 ml/min/1.73 m^2 (N= 2389) GFR 40-44 ml/min/1.73 m^2 N=548 GFR < 30 ml/min/1.73 m^2 N=120 **Procedure:** participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and calibrated to IDMS. GFR was calculated with the MDRD equation. CKD was defined according to GFR and staged according to KDOQI. ESRD	GFR > 60 ml/min/1.73 m^2 N=62066	8 years	CKD Progression to ESRD Cardiovascular mortality	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
				and death determined from registries. 9 Screening strategies for detection of CKD were compared				

Effect size:

NNTS = number needed to screen to detect 1 case of CKD stage 3-5.

Comparison of screening strategies to identify CKD Stages 3-5: Screen people with hypertension (HYP) or diabetes (DM) plus additional factors

Note that "/" means "or" – HYP/DM/age >55 years means HYP or DM or age > 55 years

Screening strategy	% found	% included	NNTS (95% CI)
HYP / DM	44.2	12.0	5.9 (5.7 to 6.2)
HYP/ DM/family history of HYP or DM	59.8	41.8	15.3 (14.8 to 15.9)
HYP/ DM/CVD	57.5	16.0	6.1 (5.9 to 6.3)
HYP/ DM/obesity/smoking	73.8	50.0	15.8 (15.2 to 16.3)
HYP/ DM/CVD/obesity/smoking/ family history of HYP or DM	81.4	66.9	19.1 (18.5 to 19.8)
HYP/ DM/age > 55 years	93.2	37.1	8.7 (8.5 to 9.0)
UK CKD guidelines (HYP/DM/CVD/moderate-severe lower UT symptoms/autoimmune disease)	60.9	19.9	8.6 (8.2 to 9.0)
US KDOQI (HYP/DM/age > 60/autoimmune disease)	89.3	29.0	8.7 (8.4 to 9.0)
ISN (screen everybody)	100	100	20.6 (20.0 to 21.2)

To achieve a high detection rate with low NNTS : screening people with HYP/DM/> 55 years old fulfils this as 93% of people with CKD Stage 3-5 are found and only 8.7 people must be screened to find 1 case of CKD.

Progression to ESRD

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
After a median follow-up of 8 years, 51/65123 people progressed to ESRD. Incidence rate was 0.04, 0.2, and 2.6 per 100 patient years for those with GFR 45-59, 30-44, and < 30, respectively. to Progression ESRD influenced by GFR: HR 1.0 for GFR 45-59 ml/min/1.73 m^2; HR 4.2 (95% CI 1.5 to 11) for GFR 30-44 ml/min/1.73 m^2 HR 68.5 (95% CI 30 to 156) for GFR < 30 ml/min/1.73 m^2 Also, male sex, diabetes, hypertension, age > 70 years significantly associated with progression to ESRD **Cardiovascular Death:** After a median follow-up of 8 years, 2604/65156 people died from cardiovascular causes. Incidence rate was 3.5 for GFR 45-59 ml/min/1.73 m^2, 7.4 for GFR 30-44 ml/min/1.73 m^2, and 10.1 for GFR < 30 ml/min/1.73 m^2 **Note:** Limitations –Cross-sectional analysis. Participants were volunteers, so may have selection bias (participation increased with increasing age) Although a European study, it was a predominantly Caucasian sample -caution in applying to areas of high ethnic diversity. Also used 1 creatinine measure to classify people to levels of renal function.								

Table 285: Haroun et al. 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. Journal of the American Society of Nephrology 2003; 14: 2934-41	Case series (longitudinal study) USA Evidence level:3 Study examined the association between hypertension and smoking and future risk of CKD	N=23 534	Participants from the CLUE study, a cancer research project involving 26000 adult volunteers. Predominantly a white population. Exclusion criteria: acute renal failure, non-residents of Washington county, subjects with incomplete records.	N=143 cases of CKD. N=51 cases of ESRD N=92 death certificate cases Risk factors of interest: systolic and diastolic blood pressure, diabetes status, smoking status, years of education. BP categorised as optimal < 120 mmHg systolic or < 80 mmHg diastolic; normal = 120-129 mmHg systolic or 80-84 mmHg diastolic; high-normal = 130-139 mmHg systolic or 85-89 mmHg diastolic; stage 1 hypertension = 140-159 mmHg systolic or 90-99 mmHg diastolic; stage 2 hypertension = 160-179 mmHg systolic or 100-109 mmHg diastolic; stage 3 or 4 hypertension ≥ 180 mmHg systolic or ≥ 110 mmHg diastolic.	n/a	20 years	Development of CKD identified by need for dialysis or death certificate notification of kidney disease. (both these were confirmed by record review, via the health care financing administration (HCFA) database)	NIH

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

Of the population (N=23 534), there were a total of 143 cases of CKD (identified by need for dialysis or death of kidney disease). 51 cases of ESRD, 92 cases of CKD-related death

CKD cases were significantly more likely to be older (p<0.001), hypertensive (p<0.001), report ever smoking cigarettes (p<0.05) and be less educated (p<0.001).

Effect of Gender on risk of developing CKD

More men than women developed CKD during the 20 year study. Women had a significantly decreased risk of developing CKD than men [adjusted HR 0.6 (95% CI 0.4 to 0.8)]

Effect of Hypertension on risk of developing CKD

The risk of developing CKD increased as blood pressure increased.

Men with stage 3 or 4 hypertension had a significantly increased risk of developing CKD than men with optimal BP control [HR 9.7 (95% CI 1.2 to 75.6)].

Women with Stage 2 hypertension had a significantly increased risk of developing CKD than women with optimal BP control [HR 6.3 (95% CI 1.3 to 29.0)].

Women with Stage 3 or 4 hypertension had a significantly increased risk of developing CKD than women with optimal BP control [HR 8.8 (95% CI 1.8 to 43.0)].

Adjusted relative hazard of CKD in CLUE population: adjusted for age, cigarette smoking, treated diabetes, and gender (where applicable).

Baseline risk factor	Men (95% CI)	Women (95% CI)	Total population (95% CI)
JNC-VI BP category*			
Optimal	1.0	1.0	1.0
Normal	1.4 (0.2-12.1)	2.5 (0.5-12.0)	1.8 (0.5-6.5)
High-normal	3.3 (0.4-25.6)	3.0 (0.6-14.4)	3.0 (0.9-10.3)
Stage 1 hypertension	3.0 (0.4-22.2)	3.8 (0.8-17.2)	3.2 (1.0-10.4)
Stage 2 hypertension	5.7 (0.8-43.0)	6.3 (1.3-29.0)	5.7 (1.7-18.9)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Stage 3 or 4 hypertension		9.7 (1.2-75.6)		8.8 (1.8-43.0)		8.8 (2.6-30.3)		
Treated diabetes, yes vs. no		5.0 (3-10)		10.7 (6-19)		7.5 (4.8-11.7)		
Current cigarette smoker, yes vs. no		2.4 (1.5-4))		2.9 (1.7-5)		2.6 (1.8-3.7)		
Gender, female vs. male						0.6 (0.4-0.8)		

*For hypertension, p<0.001 in test for trend by BP category in all groups.

Effect of Diabetes on risk of developing CKD

People treated for diabetes were at a significantly increased risk of developing CKD compared with people who were not receiving treatment for diabetes [adjusted HR 7.5 (95% CI 4.8 to 11.7)] This increased risk was seen in both males [adjusted HR 5.0 (95% CI 3 to 10)] and females [adjusted HR 10.7 (95% CI 6 to 19)]

Effect of Smoking on risk of developing CKD

Current smokers had a significantly increased risk of CKD than non-current smokers [adjusted HR 2.6 (95% CI 1.8 to 3.7)]. This increased risk was seen in both males [adjusted HR 2.4 (95% CI 1.5 to 4)] and females [adjusted HR 2.9 (95% CI 1.7 to 5)]

Attributable risk

Baseline risk factor	Attributable risk per million population
JNC-VI BP category Normal	650
High-normal	1510
Stage 1 hypertension	2650 (23% of CKD risk)
Stage 2 hypertension	1820
Stage 3 or 4 hypertension	1150
Treated diabetes	1270
Smoking	3640 (31% of CKD risk)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Assessment of bias: Adult volunteers used in the study (selection bias), only severe kidney disease identified, milder forms of CKD would not have been picked up by the chosen outcomes. BP, diabetes diagnosis and smoking status were all assessed at recruitment in 1974. No estimation of loss to follow up. Could not estimate baseline CKD in the whole cohort. They tested a subset of cases (N=85) and controls (N=175) matched for age, race, gender, hypertension, diabetes. They report that 78/85 (92%) cases and 171/175 (98%) of controls had a serum creatinine < 1.5 mg/dl. no repeated measurements of BP done during course of study, poor identification of diabetes (by medication use in medical records), volunteers (selection bias)								

Table 286: Kurella et al. 2005

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults.[see comment]. Journal of the American Society of Nephrology. 2005; 16(7):2134-2140. Ref ID: 433	Prospective cohort study USA Evidence level: 2+	N=10 096	Participants part of the Atherosclerosis Risk in Communities Study (ARIC) **Inclusion criteria:** Participants recruited randomly from 4 US communities, age 45-64 years, **Exclusion criteria:** Baseline CKD, baseline diabetes, participants with missing data for components of the metabolic syndrome, missing follow up serum creatinine measurements **Baseline characteristics:** Participants with metabolic syndrome were more likely to be slightly older (53 vs.54) , to have coronary heart disease, less likely to use alcohol or have regular physical activity. Baseline eGFR was slightly higher and as expected BP, glucose, insulin and lipid measurements were significantly different between the groups. Those excluded from the original	N=2110 Participants with the metabolic syndrome Serum creatinine measured at baseline and at 9 years follow-up. eGFR calculated using abbreviated MDRD equation. Metabolic syndrome defined as ≥3 of the following: 1) waist measurement > 88 cm for women or >102 cm for men. 2) Triglycerides ≥150 mg/dl. 3) HDL cholesterol < 50 mg/dl for women or <40 mg/dl for men. 4) BP ≥ 130/≥ 85	N=7986 Participants without the metabolic syndrome	9 years	Development of CKD (defined as eGFR < 60ml/min/ 1.73m^2 after baseline eGFR ≥ 60ml/min/ 1.73m^2)	Authors were supported by Atlantic philanthropies, NIH, Am Soc Nephrology, John A Hartford Foundation.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			cohort were more likely to be black, male, and to meet the criteria for the metabolic syndrome, they were on average 1 year older and had an eGFR 3ml/min/1.73m^2 higher.	mmHg or the use of BP medications. 5) fasting glucose ≥110 mg/dl				

Effect size

Odds ratios (OR) adjusted for age, gender, race, education, BMI, alcohol and tobacco use, coronary heart disease, physical activity.

N=691 (7%) developed CKD (GFR < 60 ml/min/1.73m^2) after 9 years follow-up.

Odds Ratio (OR) with 95% CI of developing CKD over 9 years of follow up:

	Age, gender and race adjusted	Multivariable adjusted
eGFR <60 ml/min/1.73m^2	1.53 (1.29-1.82)	1.43 (1.18-1.73)

OR of developing CKD over 9 years of follow up by individual metabolic syndrome traits

	Unadjusted	Age, gender and race adjusted
Abdominal obesity	1.27 (1.09-1.48)	1.18 (1.00-1.40)
Elevated triglycerides	1.48 (1.25-1.74)	1.34 (1.12-1.59)
Low HDL	1.19 (1.02-1.40)	1.27 (1.08-1.49)
Hypertension	2.19 (1.87-1.56)	1.99 (1.69-2.35)
Impaired fasting glucose	1.17 (0.93-1.48)	1.11 (0.87-1.40)

As the number of traits increased, there was a significant stepwise increase in risk of developing CKD. Those with 5 criteria had an OR of 2.45 (95% CI: 1.32-4.54) for developing CKD compared to those with 0 traits.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
10% of the cohort developed diabetes and 19% developed hypertension. After adjusting for the incident diabetes and hypertension, relative risk of developing CKD in the metabolic syndrome group remained significantly higher RR: 1.24 (95% CI: 1.01-1.51)								

Table 287: Munter et al. 2000

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Muntner P, Coresh J, Smith JC et al. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney International. 2000; 58(1):293-301. Ref ID: 1176	Case series (observational study) USA Evidence level: 3 Aim is to determine the association of plasma lipids with loss of renal function and the clinical onset of mild renal insufficiency	N=12 728	**Inclusion criteria:** ARIC study cohort, age 45-64, sampled from 4 US communities using probability sampling techniques. Other inclusion criteria not described in this paper. **Exclusion criteria:** Severe hypercreatinaemia at baseline, on lipid lowering medications at baseline, missing data for lipids or creatinine at baseline, or at follow up, participants who did not fast prior to blood draw, participants of races other than white and African-American. **Baseline data:** ARIC population: 45% male, 23% black, 10% diabetic, 32% hypertensive, mean age 54 years, creatinine 1.09 mg/dl, total cholesterol 215 mg/dl, triglycerides 128 mg/dl, HDL cholesterol 53 mg/dl, LDL cholesterol 135 mg/dl	Plasma lipids: Total cholesterol, HDL cholesterol (including HDL-2 and HDL-3), LDL cholesterol, apolipoprotein A-1, apolipoprotein-B, Lp(a), triglycerides		3 years	Rise in serum creatinine of ≥ 0.4 mg/dl (measured using modified kinetic Jaffe method) ≥ 25% reduction in estimated creatinine clearance (Cockroft-Gault)	Authors supported by NIH and National Centre for Research Resources ARIC study funded by National, heart, lung and blood institute.
Effect size: *Relative risks were adjusted for race, gender, age, baseline systolic BP, type of anti-hypertensive medication use, diabetes mellitus status and creatinine.								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Rise in serum creatinine of ≥ 0.4 mg/dl

Rise in serum creatinine of ≥ 0.4 mg/dl: 1.7% (191/12728) of participants; incidence rate 5.1 per 1000 person years of follow-up.

People who had a rise serum creatinine of ≥ 0.4 mg/dl were more likely to be older, black, have diabetes, hypertension, and have a higher baseline creatinine concentration.

Incidence (rate per 1000 person years) and adjusted relative risks (95% CI) of a rise in creatinine ≥ 0.4mg/dl from baseline to 3 year follow up by lipid quartiles at baseline.

Lipid	Quartile				
	1	2	3	4	P trend
Triglycerides					
Rate	4.0	3.9	5.4	7.2	0.0009
Adjusted relative risk	1.0	0.99 (0.6, 1.6)	1.31(0.9, 2.0)	1.65 (1.1, 2.5)	0.008
Lp(a)					
Rate	4.3	4.4	4.7	7.0	0.01
Adjusted relative risk	1.0	0.96 (0.6, 1.5)	0.83 (1.5, 1.3)	1.10 (0.7, 1.7)	0.70
HDL cholesterol					
Rate	6.8	5.1	5.8	2.8	0.0009
Adjusted relative risk	1.0	0.73 (0.5, 1.1)	0.86 (0.6, 1.3)	0.47 (0.3, 0.8)	0.01
HDL-2 cholesterol					
Rate	6.6	4.4	5.6	3.5	0.01
Adjusted relative risk	1.0	0.65 (0.4, 1.0)	0.84 (0.6, 1.2)	0.57 (0.4, 0.9)	0.05
HDL-3 cholesterol					
Rate	6.3	5.2	5.5	3.5	0.02
Adjusted relative risk	1.0	0.89 (0.6, 1.3)	0.99 (0.7, 1.5)	0.67 (0.4, 1.1)	0.17

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Apolipoprotein A								
Rate	6.6		4.8	5.1	4.1		0.03	
Adjusted relative risk	1.0		0.73 (0.5, 1.1)	0.79 (0.5, 1.2)	0.66 (0.4, 1.0)		0.08	

Incidence of a creatinine rise was NS associated with total cholesterol (p=0.31), LDL cholesterol (p=0.66) or apolipoprotein B (p=0.33).

People with the highest quartile of triglycerides (> 156 mg/dl) had a significantly increased risk of a rise in creatinine ≥ 0.4 mg/dl from baseline compared to people with the lowest quartile of triglycerides (< 78 mg/dl) [adjusted RR 1.65 (95% CI 1.1 to 2.5), p=0.01]

People with the highest quartile of HDL cholesterol (> 64 mg/dl) had a significantly decreased risk of a rise in creatinine ≥ 0.4 mg/dl from baseline compared to people with the lowest quartile of HDL cholesterol (< 41 mg/dl) [adjusted RR 0.47 (95% CI 0.3 to 0.8), p<0.02]

People with the highest quartile of HDL-2 cholesterol (> 20 mg/dl) had a significantly decreased risk of a rise in creatinine ≥ 0.4 mg/dl from baseline compared to people with the lowest quartile of HDL-2 cholesterol (< 9 mg/dl) [adjusted RR 0.57 (95% CI 0.4 to 0.9), p<0.02]

The RR of a rise in creatinine ≥ 0.4 mg/dl from baseline was NS for Lp (a), HDL-3 cholesterol, and apolipoprotein A.

Adjusted relative risks* (95% CI) of an incident rise in creatinine for a 3x higher baseline plasma triglyceride level overall and in selected subgroups

Overall	1.64 (1.2, 2.2)	P not stated
Non-diabetics	1.48 (1.0, 2.1)	P=0.04
Diabetics	2.44 (1.3, 4.7)	P=0.007
Normal creatinine	1.68 (1.2, 2.4)	P=0.005
African Americans	2.39 (1.5, 3.9)	P=0.001
Normotensive	1.65 (1.0, 2.7)	P=0.05
Hypertensive	1.57 (1.0, 2.4)	p=0.03

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
The adjusted relative risks for a rise in creatinine were not significant for those with hypercreatinaemia at baseline and for those who were white. **≥ 25% reduction in estimated creatinine clearance (Cockroft-Gault)** There were 407/12728 (3.2%) cases of a ≥ 25% reduction in estimated creatinine clearance during follow-up. For each three-fold higher triglycerides, the RR of developing a ≥ 25% reduction in estimated creatinine clearance was 1.51 (95% CI 1.2 to 2.0), p=0.003 (adjusted for race, gender, age, baseline systolic BP, type of anti-hypertensive medication use, diabetes mellitus status and creatinine clearance, insulin, glucose)								

Table 288: New et al. 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
New JP, Middleton RJ, Klebe B et al. Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. Diabetic Medicine. 2007; 24(4):364-369. Ref ID: 3002.	Cross-sectional population study UK population study Evidence Level: 3	N=162113	**Inclusion criteria:** General practice computer records reviewed from 17 practices in Surrey, Kent, greater Manchester area, UK between 2003 and 2004. **Exclusion criteria:** not stated **Baseline Characteristics:** a mostly Caucasian general practice UK population	Incidence of CKD in people with diabetes **Procedure:** a dataset of demographic, laboratory, diagnostic and prescription variables from patient records were extracted by Morbidity Information Query and Export Syntax between 2003 and 2004. Diabetes was identified with the Read code for diabetes. Serum creatinine values were converted to MDRD GFR and CKD was staged according to KDOQI. Hypertension defined as SBP > 140 mm Hg or DBP > 80 mm Hg.	Incidence of CKD in people without diabetes	N/A	CKD (defined as GFR < 60 ml/min/1.73m^2	Roche

Effect size:

The prevalence of diabetes in the study population was 3.1% (5072/162113).

Diabetes as a risk factor for CKD:

People with diabetes were more likely to have CKD then people without diabetes. 31.3% of people with diabetes had Stage 3-5 CKD (GFR < 60 ml/min/1.73m^2)

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

compared to 6.9% of people without diabetes (p<0.001). The higher prevalence of diabetes-associated CKD was seen at all stages of CKD. 28% of people with diabetes had Stage 3 CKD compared to 6.7% of people without diabetes had Stage 3 CKD (p<0.001).

Only 33% of diabetics with GFR 30-60 had serum creatinine values > 120 micromol/l (upper limit of normal), indicating that measuring serum creatinine level alone fails to identify Stage 3 CKD.

63% of people with diabetes and GFR < 60 ml/min/1.73m^2 had normoalbuminuria, indicating that microalbuminuria testing was insensitive and used alone is not sufficient for screening for CKD.

GFR (ml/min/1.73m^2)	% Diabetes (N=5072)	% No diabetes (N=157041)	p-value
> 90	8.3	3.1	< 0.001
60-89	41.9	13.5	< 0.001
30-59	28.9	6.7	< 0.001
15-29	2.1	0.2	< 0.001
< 15	0.3	0.03	< 0.001

Diabetes as a risk factor for anaemia:

People with diabetes were more likely to have anaemia compared with people without diabetes (5.9% vs.1.4%, p<0.001).

Management of hypertension or high cholesterol (with statins) was better in people with diabetes than in people without diabetes.

Note: Limitations – cross-sectional analysis by retrospectively reviewing medical records. Although a UK study, it was a predominantly Caucasian sample -caution in applying to areas of high ethnic mix.

Table 289: Retnakaran et al. 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Retnakaran R, Cull CA, Thorne KI et al. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes. 2006; 55(6):1832-1839. Ref ID: 3944	Prospective case series Evidence level: 3 UK study	N=5032 N Multivariate analysis= 2167	**Inclusion criteria:** UKPDS: Adults 25-65 years old with newly diagnosed type 2 diabetes and fasting plasma glucose levels ≥ 6.0 mmol/l recruited between 1977 and 1991. **Exclusion criteria:** MI stroke within preceding year, severe vascular disease, uncontrolled hypertension, proliferative/preproliferative retinopathy, plasma creatinine ≥ 175 micromol/l, treatment with steroids, severe previous illness. **Baseline data:** mean age 52 years, 60& male, 82% Caucasian, 7.6% African Caribbean, 10% Indian Asian, 30% smoker, median UAC 9 mg/l, median plasma creatinine 82 micromol/l, SBP 135 mm Hg, DBP 83 mm Hg, 45% on antihypertensive agents, 6.9% HbAC1, 19% previous CVD	N/A Procedure: patients randomly allocated therapies for glycaemic control (not described in this paper). Serum creatinine, morning urine sample tested for albumin at baseline and annually. Participants followed up to assess development of micro or macroalbuminuria or CrCl ≤ 60 ml/min/1.73 m^2	N/A	Median 15 years (Until 1997)	Development of Microalbuminuria (UAC 50-299 mg/l) Development of macroalbuminuria (UAC ≥ 300 mg/l) Development of CrCl ≤ 60 ml/min/1.73 m^2	MRC, British Diabetic Association, British Heart Foundation, Novo Nordisk, Bayer, Bristol-Myers Squibb, Hoechst, Eli Lilly

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

Multivariate analysis was restricted to N=2167. This is a loss of half of the study participants (due to incomplete data for multivariate analysis). Therefore, caution in interpreting results and EC only extracted data for risk factors where evidence was scanty.

Hazard ratios (HR) adjusted for race, gender, age, smoking status, weight, waist circumference, SBP, DBP, hypertension history, FPG, HbAC1, HOMA %B, HOMA %S, total, LDL, HDL cholesterol, triglycerides, white cell count, urine albumin, plasma creatinine, previous CVD, retinopathy, neuropathy

1544/4031 (38%) people developed albuminuria.

1449/5032 (29%) developed renal impairment (CrCl ≤ 60 ml/min/1.73 m^2 or doubling of serum creatinine).

577/4006 (14%) developed both albuminuria and renal impairment (CrCl ≤ 60 ml/min/1.73 m^2 or doubling of serum creatinine).

Of the 1534 patients who developed albuminuria, 977 (64%) did NOT develop renal impairment, 372 (24%) developed renal impairment subsequent to developing albuminuria, 12% developed renal impairment before developing albuminuria.

Risk of Developing Microalbuminuria

Of 2167 people, 756 developed microalbuminuria

In multivariate analysis of adults with type 2 diabetes (N=2167), African Caribbeans had NS risk of developing microalbuminuria compared with Caucasians [HR 1.21 (95% CI 0.89 to 1.65), p=0.22]

Indian Asians had a significantly increased risk of developing microalbuminuria compared with Caucasians [HR 2.02 (95% CI 1.59 to 2.60), p<0.0001].

Smokers had a significantly increased risk of developing microalbuminuria compared with non smokers [HR 1.20 (95% CI 1.01 to 1.42), p=0.036].

Significantly increased risk of developing microalbuminuria for UAC, SBP (10 mm Hg increase), HbAC1, TGL, white blood cell count, previous CVD.

Risk of Developing Macroalbuminuria

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Of 2167 people, 219 developed macroalbuminuria In multivariate analysis of adults with type 2 diabetes (N=2167), African Caribbeans had NS risk of developing macroalbuminuria compared with Caucasians [HR 1.05 (95% CI 0.59 to 1.86), p=0.87] Indian Asians had a significantly increased risk of developing macroalbuminuria compared with Caucasians [HR 2.07 (95% CI 1.36 to 3.15), p=0.00066]. Significantly increased risk of developing macroalbuminuria for UAC, SBP (10 mm Hg increase), HbAC1, TGL, previous CVD. **Risk of developing CrCl ≤ 60 ml/min/1.73 m^2** Of 2167 people, 584 developed CrCl ≤ 60 ml/min/1.73 m^2 In multivariate analysis of adults with type 2 diabetes (N=2167), African Caribbeans had NS risk of developing CrCl ≤ 60 ml/min/1.73 m^2 compared with Caucasians [HR 1.26 (95% CI 0.91 to 1.76), p=0.17] Indian Asians had a significantly increased risk of developing CrCl ≤ 60 ml/min/1.73 m^2 compared with Caucasians [HR 1.93 (95% CI 1.38 to 2.72), p=0.00015]. Smokers had a significantly increased risk of developing CrCl ≤ 60 ml/min/1.73 m^2 compared with non smokers [HR 1.25 (95% CI 1.03 to 1.52), p=0.022]. Significantly increased risk of developing CrCl ≤ 60 ml/min/1.73 m^2 for UAC, SBP (10 mm Hg increase), previous retinopathy Authors suggest that albuminuria does not always predict renal impairment and albuminuria and renal impairment may not reflect the same underlying pathology of T2D. Note that ACE inhibitors usage not assessed.								

Table 290: Seaquist et al. 1989

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Seaquist ER, Goetz FC, Rich S et al. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med. 1989; 320(18):1161-1165. Ref ID: 3892	Case series, USA Evidence level: 3 to investigate the incidence of nephropathy in the diabetic siblings of diabetics with nephropathy and the siblings of diabetics without it.	N= 37 probands N=41 siblings of the probands	Probands were diabetic patients that did or did not have diabetic nephropathy Patients recruited from a university diabetics centre in Minnesota, USA **Inclusion criteria:** Minimum duration of Type 1 diabetes of 10 years in probands and 7 years in siblings. B**aseline characteristics:** There were no significant differences between groups with respect to duration of diabetes, age at onset, numbers of siblings.	Diabetic Siblings of Proband diabetics with nephropathy N= 29	Diabetic Siblings of probands without nephropathy N=12	n/a	24 hr urinary albumin ESRD	NIH Minnesota medical foundation
Effect size: Prevalence of nephropathy in the siblings of diabetics: Without nephropathy: 17% (2/12) With nephropathy: 83% (24/29) p<0.001								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Presence of ESRD in the siblings of diabetics Without nephropathy: 0% (0/12) With nephropathy: 41% (12/29) There was NS difference in the duration of diabetes in either group of siblings. Among siblings without ESRD, the only factor found to be significant in predicting nephropathy in the diabetic siblings was the presence of nephropathy in the diabetic probands (p=0.03) **Assessment of bias:** Confounders like the effect of environmental factors (smoking, diet, etc) that might have been shared by the siblings is not controlled for.								

Table 291: Speckman et al. 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Speckman RA, McClellan WM, Volkova NV et al. Obesity is associated with family history of ESRD in incident dialysis patients. American Journal of Kidney Diseases. 2006; 48(1):50-58. Ref ID: 3959	case series Evidence level: 3 US study	N ESRD total = 23822 N ESRD No family history ESRD =18369 N ESRD with family history of ESRD= 5453	**Inclusion criteria:** Family History of ESRD Study: patients ≥ 20 years old with ESRD initiating RRT in dialysis units in North Carolina, South Carolina, and Georgia between 1995 and 2003. **Exclusion criteria:** Patients residing in other states, known Mendelian cause of ESRD (polycystic kidney disease, Alport syndrome), urological conditions, surgical nephrectomy, patients missing data on primary cause of ESRD or serum creatinine concentration, ethnicities other than black or white **Baseline data:** Compared with those who reported no family history of ESRD, patients reporting a family history of ESRD had significantly greater mean BMI (28.2 vs.26.6 kg/m^2),	Assessed effect of BMI, race, smoking, hypertension, diabetes on odds of having a family history of ESRD. **Procedure:** Participation of patients initiating RRT was voluntary. A family history of ESRD was considered present if an incident ESRD patient reported having either a first-degree (parent, child, sibling) or second-degree (grandparent, aunt, uncle, grandchild, or half-sibling) relative with ESRD. ESRD defined at dialysis, kidney transplant, or death from kidney disease before dialysis was started. A standardised data-collection instrument was used to collect data on presence of ESRD in first and second degree relatives, total number of siblings and	N/A	N/A	A family history of ESRD	None required

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			were younger (57 vs.61 years), had more first degree relatives with ESRD (8.7 vs.7.6), were more likely to be black (74.5% vs.52.2%), and more likely to be female (56% vs.49%)	children. Age, sex, race, weight, height of patients, primary cause of ESRD, co morbidities, laboratory results at dialysis initiation obtained from Centres for Medicare and Medicaid Services Form 2728.				

Effect size:

Odds ratios (OR) adjusted for race, gender, age, history of diabetes, history of hypertension, cause of ESRD, smoking status, number of first-degree relatives, and estimated GFR.

5453/23822 (22.9%) people with ESRD reported having a family history of ESRD.

In crude analysis, hypertension, diabetes, female gender, black ethnicity, and obesity were all associated with increased odds of a family history of ESRD.

There was a high prevalence of obesity among patients with ESRD: 6.7% were underweight, 37.8% had a normal BMI, 27.6% were overweight, 15.2% were obese, and 12.5% were morbidly obese.

Effect of BMI on odds of a family history of ESRD

There was NS differences in the odds of reporting a family history of ESRD for underweight patients with ESRD (N=1599, BMI < 18.5 kg/m^2) compared with normal weight people with ESRD (N=9037, BMI 18.5-24.9 kg/m^2).

Overweight people with ESRD (N=6584, BMI 25-29.9 kg/m^2) had a 17% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (N=9037, BMI 18.5-24.9 kg/m^2) [adjusted OR 1.17 (95% CI 1.08 to 1.26), p < 0.001]

Obese people with ESRD (N=3624, BMI 30-34.9 kg/m^2) had a 25% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (N=9037, BMI 18.5-24.9 kg/m^2) [adjusted OR 1.25 (95% CI 1.14 to 1.37), p < 0.001]

Morbidly obese people with ESRD (N=2978, BMI ≥ 35 kg/m^2) had a 40% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (N=9037, BMI 18.5-24.9 kg/m^2) [adjusted OR 1.40 (95% CI 1.27 to 1.55), p < 0.001].

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect of Race on odds of a family history of ESRD

Black people with ESRD (N=13645) were significantly more likely to report a family history of ESRD than white people with ESRD (N=10127) [adjusted OR 2.38 (95% CI 2.21 to 2.55), p<0.001]

Effect of Hypertension on odds of a family history of ESRD

People with ESRD and a history of hypertension (N=19987) were significantly more likely to report a family history of ESRD than people with ESRD and no history of hypertension (N=3835) [adjusted OR 1.12 (95% CI 1.02 to 1.23), p<0.001]

Effect of Smoking on odds of a family history of ESRD

There was NS differences in the odds of reporting a family history of ESRD for patients with ESRD and a history of smoking (N=2078) compared with people with ESRD and no history of smoking (N=21744) [adjusted OR 1.01 (95% CI 0.90 to 1.14), p=0.851]

Effect of diabetes on odds of a family history of ESRD

There was NS differences in the odds of reporting a family history of ESRD for patients with ESRD and a history of diabetes (N=4966) compared with people with ESRD and no history of diabetes (N=11174) [adjusted OR 1.09 (95% CI 0.96 to 1.23), p=0.184]

Note: characteristics of participants NS different from non-participants, NS also for BMI levels. Weight measurement in those reporting family history of ESRD may be confounded by edema

Table 292: Stengel et al. 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Stengel B, Tarver CM, Powe NR et al. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology. 2003; 14(4):479-487. Ref ID: 786	Retrospective case series USA Evidence Level: 3	N=9082	**Inclusion criteria:** NHANES II a general health survey was conducted the USA in 1976-1980. **Exclusion criteria:** ESRD at baseline, people with "heterogeneous" risk of CKD, non-white or non-African Americans **Baseline Characteristics:** mean age 49.3 years, mean eGFR 88.1 ml/min, 47% male, 10% African American, 4% diabetic, 6% CVD history, 49% hypertensive, 36% smokers, 26% former smokers, 46% normal BMI (18.5-24 kg/m^2), 35% overweight (25-29 kg/m^2), 12% obese (30-34 kg/m^2), 5% morbidly	**Procedure:** participants in completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the MDRD equation. Physical activity, alcohol consumption, and smoking habits were documented in the health questionnaire. Exercise habits were described as "very active, moderately active or inactive. For smoking habits, people were classified as non-smokers, former smokers, or smokers. Smokers were classified into 2 categories ≤ 20 cigarettes/day or > 20 cigarettes/day. Alcohol consumption was classified as never, seldom (< once/week), weekly (1-6 times/week), or daily (1 or	Effect of smoking on CKD risk Effect of exercise on CKD risk Effect of alcohol consumption on CKD risk	Mean 13.2 years	Risk of CKD-related death Risk of ESRD	National Centre for Health Statistics

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			obese (BMI > 35)	more times/day). CKD-related deaths were identified by computerised matching to the National Death Index and Social Security Administration Death Master Files databases (1976-1992). Participants with ESRD were identified by computer name matching from the Medicare registry.				

Effect size:

Relative risks (RR) were adjusted for age, gender, race, diabetes, CVD, hypertension, SBP, cholesterol, GFR

189 (total N=9082) subjects developed CKD and 23% of these were treated for ESRD. Of 189 CKD cases, 12% died of CKD, while 64% died with CKD being a contributing cause of death. Of the 189 CKD cases, 23% were diabetic or hypertensive nephropathy, while 77% were other types of CKD.

Physical Inactivity as a risk factor for CKD:

People with low physical activity have a significantly increased risk of CKD compared to people who have high physical activity [adjusted RR 2.2 (95% CI 1.2 to 4.1)].

People with moderate physical activity have NS risk of CKD compared to people who have high physical activity [adjusted RR 1.2 (95% CI 0.7 to 2.0)].

Smoking as a risk factor for CKD:

Smokers (> 20 cigarettes/day) have a significantly increased risk of CKD compared to non-smokers [adjusted RR 2.6 (95% CI 1.4 to 4.7)].

Smokers (1-20 cigarettes/day) have NS risk of CKD compared to non-smokers [adjusted RR 0.9 (95% CI 0.5 to 1.9)].

Former smokers have NS risk of CKD compared to non-smokers [adjusted RR 0.8 (95% CI 0.5 to 1.2)].

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Alcohol consumption as a risk factor for CKD: People who drank alcohol daily had NS risk of CKD compared to people who never drank alcohol [adjusted RR 0.9 (95% CI 0.6 to 1.3)]. People who drank alcohol weekly had NS risk of CKD compared to people who never drank alcohol [adjusted RR 0.9 (95% CI 0.4 to 2.2)]. People who seldom drank alcohol had NS risk of CKD compared to people who never drank alcohol [adjusted RR 0.5 (95% CI 0.3 to 1.0)]. **Body Mass Index as a risk factor for CKD:** Thin people (BMI < 18.5 kg/m^2) had NS risk of CKD compared to people with a normal BMI (18.5-24 kg/m^2) [adjusted RR 1.0 (95% CI 0.2 to 3.8)]. Overweight people (BMI 25-29 kg/m^2) had NS risk of CKD compared to people with a normal BMI (18.5-24 kg/m^2) [adjusted RR 0.7 (95% CI 0.4 to 1.3)]. Obese people (BMI 30-34 kg/m^2) had NS risk of CKD compared to people with a normal BMI (18.5-24 kg/m^2) [adjusted RR 0.7 (95% CI 0.4 to 1.4)]. Morbidly obese people (BMI > 35 kg/m^2) had NS risk of CKD compared to people with a normal BMI (18.5-24 kg/m^2) [adjusted RR 1.7 (95% CI 0.6 to 4.5)].								

Table 293: Tillin et al. 2005

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Tillin T, Forouhi N, McKeigue P et al. Microalbuminuria and coronary heart disease risk in an ethnically diverse UK population: A prospective cohort study. Journal of the American Society of Nephrology. 2005; 16(12):3702-3710. Ref ID: 3475	cohort study UK Evidence Level: 2 -	N total = 2965 N=1460 white Europeans N=946 South Asians and N=559 African Caribbean's 27% of participants had no AER measurement	Patients recruited from two population based studies in West London. Recruitment was from ethnicity and gender stratified random samples from the general practitioner practice lists. **Inclusion criteria**: Age 40-69 years, other criteria of the individual studies not mentioned here. Of the patients for whom AER measurements were not available (27%), there were significant differences in gender, prevalence of current/former smoking, and CHD mortality. **Baseline Characteristics:** South Asians and African Caribbeans were more likely to be glucose intolerant and insulin resistant and have higher BP than Europeans. South Asians had adverse lipid profiles, while African-Caribbeans had favourable lipid profiles.	Rates of microalbuminuria in different ethnic groups (European, South Asian and African-Carribean) and Gender	Procedure: Participants completed health questionnaire and BP, ECG, fasting blood triglycerides, cholesterol, HDL cholesterol, glucose, insulin determined as local hospital. Urine albumin was measured from timed overnight urine collections by immunoturbidometry.	Not mentioned	Mortality and cause of death Urine albumin excretion rate (AER)	British Heart Foundation
Effect size:								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Prevalence of microalbuminuria by gender and ethnicity								
			Microalbuminuria (AER 20-199 microg/min) (95%CI)					
Ethnicity			**Men**		**Women**			
European			5.9 (4.5 to 7.4)		2.7 (1.2 to 4.1)			
South Asian			6.0 (4.2 to 7.7)		2.7 (0.4 to 5.0)			
African-Caribbean			6.8 (3.9 to 9.8)		7.3 (4.3 to 10.3)			
The prevalence of microalbuminuria (AER 20-199 microg/min) was greatest in African-Caribbean and equivalent between European and South Asians. The prevalence of microalbuminuria was greater in men compared to women.								
AER geometric means (adjusted for age, fasting glucose, glucose tolerance category, SBP, BMI and manual occupation)								
Ethnicity			**Geometric mean (95% CI)**					
			Men	**P**	**Women**	**P**		
European			4.8 (4.5 to 5.0)	Reference group	3.7 (3.3 to 4.1)	Reference group		
South Asian			4.1 (3.9 to 4.4)	0.001	3.7 (3.2 to 4.4)	0.94		
African-Caribbean			5.7 (5.2 to 6.3)	0.002	5.6 (4.9 to 6.3)	<0.001		
AER (µg/min) by height/weight								
	Men				**Women**			
Ethnicity	**Short for weight**		**Not short for weight**	**P**	**Short for weight**	**Not short for weight**	**P**	
European	5.20		4.41	0.02	-	-	No association	
South Asian	5.58		4.06	<0.001	4.72	3.01	0.017	
African-Caribbean	-		-	No association	-	-	No association	
Other cardiovascular risk factors did not account for the ethnic differences in AER.								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
This study further examine the relationship between AER and CHD prevalence and mortality by ethnic groups, however these results are not presented in this evidence table. **Assessment of bias:** 27% of the cohort did not have AER measurements; there were significant differences between those whose data were included and those who weren't. The study was aimed at assessing the relationship between MA and CHD, not ethnicity and the development of CKD.								

Q.5.6 Defining progression (2014 guideline - chapter 7.2)

Table 294: Ref ID: 3882 [Fliser et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fliser D, Franek E, Joest M et al. Renal function in the elderly: impact of hypertension and cardiac function. Kidney International. 1997;	Cross-sectional study Germany Evidence level: 3	N young healthy subjects =24 N elderly healthy subjects = 29 N elderly hypertensive subjects =	**Inclusion:** healthy young subjects recruited from Heidelberg University, elderly normotensive subjects recruited from Academy for Elderly in Heidelberg, elderly hypertensive (BP > 140/90 mm Hg on three occasions) without signs of atherosclerotic vascular disease and/or heart failure were recruited from University of Heidelberg (nephrology dept), elderly with confirmed mild or moderate heart failure recruited from Cardiology department. **Exclusions:** suspected renal disease	N elderly healthy subjects = 29 N elderly hypertensive subjects = 25 N elderly heart failure subjects = 14 **Procedure:** Young and elderly healthy subjects were matched for body weight. Subjects provided	N young healthy subjects =24	N/A	GFR	Paul-Martini-Stiftung

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
51(4):1196-1204. Ref ID: 3882		25 N elderly heart failure subjects = 14	determined by sonography, urinalysis, serum chemistry **Population baseline characteristics:** Elderly hypertensive people (age 70 years) had significantly higher BMI, 24-h MAP than young (age 26 years) and elderly healthy (age 68 years) subjects. Cholesterol and triglycerides were higher in all three elderly groups compared with young healthy people. The mean age of elderly heart failure subjects was 69 years.	24-h urine collections to determine urinary albumin, creatinine clearance. GFR measured by inulin clearance.				

Effect size:

Mean GFR (inulin clearance) was significantly lower in elderly healthy people (103 ml/min/1.73m^2, N=29, mean age 68 years) compared with young healthy people (121 ml/min/1.73m^2 N=24, mean age 26 years, p<0.05)

Mean GFR (inulin clearance) was significantly lower in elderly hypertensive people (103 ml/min/1.73m^2, N=25, mean age 70 years) compared with young healthy people (121 ml/min/1.73m^2 N=24, mean age 26 years, p<0.05)

Mean GFR (inulin clearance) was significantly lower in elderly people with heart failure (92 ml/min/1.73m^2, N=14, mean age 69 years) compared with young healthy people (121 ml/min/1.73m^2 N=24, mean age 26 years, p<0.05)

Mean GFR (inulin clearance) was significantly lower in elderly people with heart failure (92 ml/min/1.73m^2, N=14, mean age 69 years) compared with elderly healthy (103 ml/min/1.73m^2, N=29, mean age 68 years) or elderly hypertensive (103 ml/min/1.73m^2, N=25, mean age 70 years) people (p<0.05)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mean GFR was NS different between elderly healthy and elderly hypertensive people. GFR was significantly affected by age a ($p< 0.001$) and heart failure ($p<0.01$), but not by MAP or BMI.								

Table 295: Ref ID: 3870 [Halbesma et al. 2006]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Halbesma N, Kuiken DS, Brantsma AH et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006; 17(9):2582-2590. Ref ID: 3870	Posthoc analysis cohort study PREVEND cohort study Groningen, Netherlands Evidence level: 2+	N total = 8592 N macroalbuminuria (≥ 300 mg/24-h) = 134 N erythrocyturia (> 250/microL, absence of leukocyturia) = 128 N impaired renal function (5% lowest CrCl/MDRD GFR) = 103	**Inclusion:** PREVEND study: adults 28-75 years old of Groningen, Netherlands. All individuals with urinary albumin concentration ≥ 10 mg/L and a random sample of people with urinary albumin concentration < 10 mg/L formed a cohort that was enriched for albuminuria. **Exclusion criteria:** insulin use, pregnancy, **Population baseline characteristics:**	N macroalbuminuria (>300 mg/24-h) = 134 N erythrocyturia (> 250/microL) = 128 N impaired renal function (5% lowest CrCl/MDRD GFR) = 103 **Procedure:** Subjects submitted two consecutive 24-h urine collections at baseline. A second screening was performed after 4 years follow-up. History of CVD was a self-assessed history of MI, cerebrovascular accident, or peripheral vascular disease. Plasma and urinary creatinine, cholesterol, glucose determined by an	Total population N=8592	4.2 years	Mortality Cardiovascular morbidity Decline in GFR	Dutch Kidney Foundation

	Total population	Macroalbuminuria	Erythrocyturia	Impaired renal
N	8592	134	128	103
Age	49	58 *	51	61 *
% Male	50	66 *	34 *	51
% History of CVD	9.4	29.7 *	13.9	30.5 *

Reference	Study type	Number of patients	Patient characteristics					Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			% UAC < 10 mg/L	30.2	0*	21.9 *	16.5 *	automated enzymatic method. Urinary leukocyte and erythrocytes measured with Nephur-test + leuco sticks. Urinary albumin concentration determined by nephelometry. Data on antihypertensive medication use from pharmacy databases. Death and morbidity statistics from the National Central Bureau of Statistics and PRISMANT databases, respectively. GFR was calculated as a mean of the creatinine clearance from the two 24-h urine collections as well as with the MDRD equation.				
			Median UAE (mg/d)	9.5	549*	23.7	37.6 *					
			% Macroalbuminuria	1.6	100*	7.0 *	17.5 *					
			% Erythrocyturia	1.5	6.7 *	100 *	7.8 *					
			GFR	80.8	68.4 *	74.9 *	44.6 *					
			* p<0.01 versus total population – specific group									
Effect size: Hazard ratios (HR) adjusted for age and sex.												

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
80% of the total population completed 4 years follow-up, whereas only 64% of those with macroalbuminuria, 76% of those with erythrocyturia, and 66% of those with impaired renal function completed the follow-up. The prevalence of macroalbuminuria in the general population of Groningen (taking into account that the study cohort was enriched for albuminuria) was 0.6%. The prevalence of erythrocyturia in the general population of Groningen (taking into account that the study cohort was enriched for albuminuria) was 1.3%. The prevalence of impaired renal function in the general population of Groningen (taking into account that the study cohort was enriched for albuminuria) was 0.9%. Venn diagram showed little overlap of macroalbuminuria, erythrocyturia, impaired renal function. 2.8% died in the total cohort (140/8592), whereas 9.7% of people with macroalbuminuria (13/134) died. 5.5% (7/128) of people with erythrocyturia died and 16.8% (17/103) of people with impaired renal function died. **Cardiovascular mortality** Compared to the total population (N=8592), people with macroalbuminuria (N=134) had a significantly increased risk of cardiovascular mortality [adjusted HR 2.6 (95% CI 1.1 to 6.0)] Compared to the total population (N=8592), people with impaired renal function (N=103) had a significantly increased risk of cardiovascular mortality [adjusted HR 3.4 (95% CI 1.5 to 8.0)] There were no cardiovascular deaths in people with erythrocyturia. **Non-Cardiovascular mortality** Compared to the total population (N=8592), people with macroalbuminuria (N=134) had NS risk of non-cardiovascular mortality [adjusted HR 1.5 (95% CI 0.7 to 3.0)] Compared to the total population (N=8592), people with impaired renal function (N=103) had a significantly increased risk of non-cardiovascular mortality [adjusted HR 3.0 (95% CI 1.6 to 5.6)] Compared to the total population (N=8592), people with erythrocyturia (N=128) had a significantly increased risk of non-cardiovascular mortality [adjusted HR 2.6 (95% CI 1.2 to 6.0)]								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Cardiovascular Morbidity

Compared to the total population (N=8592), people with macroalbuminuria (N=134) had NS risk of cardiovascular morbidity [adjusted HR 1.4 (95% CI 1.0 to 2.1)]

Compared to the total population (N=8592), people with erythrocyturia (N=128) had NS risk of cardiovascular morbidity [adjusted HR 1.4 (95% CI 0.7 to 2.5)]

Compared to the total population (N=8592), people with impaired renal function (N=103) had a significantly increased risk of cardiovascular morbidity [adjusted HR 2.3 (95% CI 1.5 to 3.4)]

GFR decline

After 4.2 years follow-up, the decline in GFR was significantly greater in subjects with macroalbuminuria (N=86, GFR decline 7.2 ml/min/1.73 m^2) compared with the general population (N=6894, GFR decline 2.3 ml/min/1.73 m^2) p<0.01.

Interestingly, the decline in GFR was significantly less in subjects with impaired renal function (N=68, GFR decline 0.2 ml/min/1.73 m^2) compared with the general population (N=6894, GFR decline 2.3 ml/min/1.73 m^2) p<0.01.

There was NS difference in the decline in GFR between the general population (N=6894, GFR decline 2.3 ml/min/1.73 m^2) and those with erythrocyturia (N=97, GFR decline 2.6 ml/min/1.73 m^2).

Sensitivity analysis: there were more diabetics in the macroalbuminuric group than the general population. Excluding diabetics did not alter the GFR decline of the macroalbuminuric group, nor did the incidence rates of mortality or morbidity change significantly.

Note: limitations: large drop-out rate in macroalbuminuria, impaired renal function, and erythrocyturia groups (and already small sizes at baseline). Authors note that baseline characteristics of those who were lost to follow-up were NS different from subjects who completed follow-up. Also state that people who are in poor health are more likely to not complete follow-up for many reasons. Caution in generalising results to non-Caucasian populations, other unknown confounding variables, survival bias (people with greater odds of progressing may have died before end of follow-up) may have been an issue, but sensitivity analysis of worst case scenario could not fully explain the observed differences in GFR decline.

Table 296: Ref ID: 17 [Hemmelgarn 2006]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hemmelgarn BR, Zhang J, Manns BJ et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006; 69(12):2155-2161. Ref ID: 17	Prospective longitudinal study Evidence level: 3 Canadian cohort	N = 10184 N mild CKD GFR 60–89 ml/min/1.73 m^2 = 6573 N moderate CKD GFR 30-59 ml/min/1.73 m^2 = 3191 N severe CKD GFR < 30 ml/min/1.73 m^2 = 420	**Inclusion:** adults ≥ 66 years with one or more serum creatinine measurements during each of two time periods: July – December, 2001 as well as July – December, 2003. Participants were identified from Calgary Laboratory Services database, Canada. **Exclusion criteria:** laboratory measurements associated with a hospital admission, dialysis patients at entry, subjects with more than 12 creatinine measurements in either of the 6 month observation periods, subjects who underwent renal transplant prior to July 1, 2003, subjects with GFR > 90 ml/min/1.73 m^2 **Population baseline characteristics:** people with	N GFR 60–89 ml/min/1.73 m^2 = 6573 N GFR 30-59 ml/min/1.73 m^2 = 3191 N GFR < 30 ml/min/1.73 m^2 = 420 **Procedure:** Serum creatinine measurements were performed in one laboratory. The first serum creatinine measurement (July 1-Dec. 31, 2001) defined the index GFR. The study mean eGFR (not the index GFR) was used to stratify people into mild, moderate or severe CKD. Data on age, sex, co-existing diseases, drug prescriptions was obtained from medical databases. Drug data was used to	Compared GFR decline within each GFR stratum in men and women with and without diabetes mellitus	2 years	Decline in GFR	Kidney Foundation of Canada, Alberta Heritage Foundation for Medical Research, Canadian Institute of Health Research

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			moderate or severe kidney disease were older (77 versus 75), more likely to be female (62% vs.55% female), and have a significantly higher comorbidity scores (3468 vs.2143) and diabetes (31% diabetes vs.14%) than people with mild CKD.	identify subjects with diabetes, as well as to calculate a Chronic Disease Score. Death and dialysis statistics were obtained from Alberta Bureau of Vital Statistics and Southern Alberta Renal Program databases, respectively. GFR calculated with MDRD equation.				

Effect size

A mixed effects model adjusting for age, sex, diabetes, and comorbidity score was used to determine rate of GFR decline.

The rate of GFR decline was greatest in people with diabetes.

Older males with diabetes had a GFR decline of 2.7 ml/min/1.73 m^2/year (95% CI 2.3 to 3.1).

Older males without diabetes had a GFR decline of 1.4 ml/min/1.73 m^2/year (95% CI 1.2 to 1.6).

Older females with diabetes had a GFR decline of 2.1 ml/min/1.73 m^2/year (95% CI 1.8 to 2.5).

Older females without diabetes had a GFR decline of 0.8 ml/min/1.73 m^2/year (95% CI 0.6 to 1.0).

The rate of GFR decline increased with decreasing GFR and the largest decline in GFR was observed in people with severe CKD GFR < 30 ml/min/1.73 m^2. (no N values given for subgroup analysis)

	Age-adjusted rate of GFR decline (ml/min/1.73 m^2/year)		
Population	**mild CKD GFR 60–89 ml/min/1.73 m^2**	**Moderate CKD GFR 30–59**	**severe CKD GFR < 30 ml/min/1.73 m^2**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				ml/min/1.73 m^2				
Females without diabetes			0.6 (95% CI 0.3 to 0.9)	1.1 (95% CI 0.8 to 1.4)		1.8 (95% CI 1.2 to 2.4)		
Females with diabetes			1.6 (95% CI 1.0 to 2.1)	2.8 (95% CI 2.3 to 3.3)		2.9 (95% CI 2.2 to 3.7)		
Males without diabetes			1.1 (95% CI 0.8 to 1.4)	1.9 (95% CI 1.5 to 2.3)		2.0 (95% CI 1.3 to 2.7)		
Males with diabetes			2.1 (95% CI 1.6 to 2.6)	3.6 (95% CI 3.1 to 4.2)		3.2 (95% CI 2.3 to 4.0)		
Similar trends were observed for the absolute change in GFR (mean GFR 2001 – mean GFR 2003) as well as for the percent change in mean GFR. When categorized by the change decline in GFR (GFR decline ≤ 0, 1-5, 6-10, 11-15, or > 15 ml/min/1.73 m^2/year), more than half of the subjects declined by 0-5 ml/min/1.73 m^2/year. This was seen in mild, moderate, or severe CKD patients. Few subjects in this older cohort experienced a rapid progression of CKD (decline in GFR > 15 ml/min/1.73 m^2/year) : 14% of mild, 13% of moderate, and 9% of severe CKD subjects had a decline in GFR > 15 ml/min/1.73 m^2/year. **Note:** limitations: caution in generalising results to non-Caucasian or to people < 66 years, other confounding variables (proteinuria, BP, cause of CKD, smoking status, lipid levels) were not taken into account, survival bias (people with greater odds of progressing may have died before end of follow-up) may have been an issue, but sensitivity analysis comparing GFR decline in people who died with those who survived showed similar rates of GFR decline, 2 years follow-up may not be enough time to assess GFR decline (although authors refute this)								

Table 297: Ref ID: 3883 [Lindeman et al. 1984]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. Kidney Int. 1984; 26(6):861-868. Ref ID: 3883	Observational study Evidence level: 3 Baltimore Longitudinal Study of Aging US cohort study	N total = 446 Males N Category 1 males (Renal or urinary tract disease) = 118 N Category 2 males (Hypertension/edematous disorder) = 74 N Category 3 males (healthy) = 254	**Inclusion:** Baltimore Longitudinal Study of Aging: self-recruited males age 22-97 with 5+ serial creatinine clearance determinations in 1958 to 1981. Subjects assigned to Category 1 (renal/UT disease) had history of UTI, significant urinary retention and/or obstructive lesions, hematuria, proteinuria, nephrolithiasis, or on a clinic visit showed proteinuria +1, > 10 WBC/hpf, > 10 RBC/hpf, presence of > 6 casts/lpf. Subjects assigned to Category 2 (Hypertension/edematous disorder) were those treated with diuretics, antihypertensives. Subjects assigned to Category 3 (healthy) were those not assigned to Category 1 or 2. **Population baseline characteristics:** Category | Category | Category N: 118 | 74 | 254 Age, years: 59.2 | 57.3 | 56.4	N Category 1 males (Renal or urinary tract disease) = 118 N Category 2 males (Hypertension/edematous disorder) = 74 **Procedure**: Subjects were assessed at baseline and every 12 - 18 months with clinical, psychological, and physiological tests at the Gerontology Research Centre. Subjects were placed in one of three categories: Category 1 (renal or urinary tract disease), Category 2 (hypertension or edematous disorder), or Category 3 (healthy). A non-fasting serum creatinine sample was obtained on arrival at the centre, and a 24-h urine collection was begun. A fasting serum creatinine	N Category 3 males (healthy) = 254	8 years	Decline in creatinine clearance with increasing age Decline in creatinine clearance with increasing MAP.	Not stated

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Creatinine clearance, ml/min	125.8	135.2	129.9	sample was obtained the next morning. True creatinine was measured by treating acid tungstate filtrates of serum with Lloyd's reagent and acid picrate buffer to remove non-creatinine chromogens. Creatinine was eluted with alkaline picrate and measured colorimetrically (100% ± 1.7 recovery) Creatinine clearance (ml/min/1.73m^2) was determined as the mean of the two samples. BP was measured at every visit.				
			SBP, mm Hg	133.0	143.1	128.4					
			DBP, mm Hg	83.6	89.7	79.9					
			MAP, mm Hg	100.1	107.5	96.1					

Effect size:

Subjects were separated into 3 different categories to avoid bias of increased BP on renal decline.

Decline in creatinine clearance

Creatinine clearance values in all three categories by age (cross-sectional data)

Age, years	N	Mean Creatinine clearance (ml/min/1.73m^2)	MAP, mm Hg
20-29.9	3	151.8	96.5
30-39.9	36	154.8	95.0
40-49.9	104	144.4	95.8
50-59.9	122	134.3	99.3
60-69.9	86	122.3	101.2

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
70-79.9			81	107.0		102.1		
80-89.9			13	91.9		100.5		
90-99.9			1	32.0		100.7		

In the whole population, creatinine clearance was stable in men < 40 years old (N=39). Creatinine clearance then declined steadily in men age 40 to 60 years (N=226). After age 60, creatinine clearance declined steeply (N= 181).

The mean cross-sectional change in creatinine clearance was: - 0.87 (ml/min/year).

Creatinine clearance values in males (longitudinal analysis)

The trend for decreasing creatinine clearance with increasing age was also observed in each Category 1, 2, and 3.

For healthy men (N=254, category 3), creatinine clearance decreased by 0.75 ml/min/year.

For men with renal disease or urinary tract disease (N=118, Category 1), creatinine clearance decreased by 1.10 ml/min/year. (NS difference compared to healthy population)

For men taking antihypertensive drugs (N=74, Category 2), creatinine clearance decreased by 0.92 ml/min/year. (NS difference compared to healthy population)

Effect of BP on decline in creatinine clearance

Renal function decreased more rapidly as MAP increased. For all subjects (N=446), the regression coefficient for change in creatinine clearance vs.MAP was -0.052 ml/min/year. This means that for every 1 mm Hg increase in MAP, the creatinine clearance decreases by 0.052 ml/min/year ($p<0.0001$).

Subgroup analysis showed that for men with renal disease or urinary tract disease (N=118, Category 1), creatinine clearance decreased by 0.076 ml/min/year for every 1 mm Hg increase in MAP ($p<0.001$).

Subgroup analysis showed that for men taking antihypertensive drugs (N=74, Category 2), creatinine clearance decreased by 0.060 ml/min/year for every 1 mm Hg increase in MAP (NS negative correlation between decline in CrCl and MAP in this group).

Subgroup analysis showed that for healthy men (N=254, category 3), creatinine clearance decreased by 0.048 ml/min/year for every 1 mm Hg increase in MAP ($p<0.001$).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
At MAP < 107 mm Hg cut-off, the effect of MAP on creatinine clearance decline is NS. **Note:** limitations: inulin clearance would have been a better measure of renal function, caution in generalising results to females								

Table 298: Ref ID: 3880 [Rowe et al. 1976]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rowe JW, Andres R, Tobin JD et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol. 1976; 31(2):155-163. Ref ID: 3880	Community based cross-sectional and longitudinal observational study Evidence level: 3 Baltimore Longitudinal Study of Aging US cohort study	N = 548 healthy males	**Inclusion:** self-recruited healthy males age 17-96 participating in Baltimore Longitudinal Study of Aging from July 1, 1961 to June 30, 1971. **Exclusion criteria:** to achieve a healthy population for study, subjects with the following diseases were excluded: nephrolithiasis, UTI, gout, prostatectomy, congestive heart failure, coronary heart disease, cerebrovascular disease, diabetes, abnormal urinalysis (proteinuria +1, 5 WBC/hpf, 5 RBC/hpf, presence of any RBC casts or granular casts), renal disease (any), diuretic or antihypertensive drug use, digitalis preparation, sex or adrenal steroid use, vasodilator use, amphetamine use	**Procedure:** Subjects were assessed at baseline and every 12 - 18 months with clinical, psychological, and physiological tests at the Gerontology Research Centre. A non-fasting serum creatinine sample was obtained on arrival at the centre, and a 24-h urine collection was begun. A fasting serum creatinine sample was obtained the next morning. True creatinine was measured by treating acid tungstate filtrates of serum with Lloyd's reagent and acid picrate buffer to remove non-creatinine chromogens. Creatinine was eluted with alkaline picrate and measured colorimetrically (100% ± 1.7 recovery) Creatinine clearance (ml/min/1.73m^2) was	The decline in creatinine clearance with increasing age	10 years	Decline in creatinine clearance with age	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Population baseline characteristics: not stated	determined as the mean of the two samples.				

Effect size:

Creatinine clearance values in healthy males (cross-sectional data)

Age, years	N	Mean Creatinine clearance (ml/min/1.73m^2)	Mean Serum creatinine concentration (mg/100 ml)
17-24	10	140.2	0.808
25-34	73	140.1	0.808
35-44	122	132.6	0.813
45-54	152	126.8	0.829
55-64	94	119.9	0.837
65-74	68	109.5	0.825
75-84	29	96.9	0.843

Creatinine clearance was stable in healthy men < 35 years old (N=83). Creatinine clearance then declined steadily in healthy men age 35 to 65 years (N=368). After age 65, creatinine clearance declined steeply (N= 97).

Linear regression analysis of creatinine clearance vs.age gave an overall slope (creatinine clearance decline) of -0.80 ml/min/1.73m^2/year.

Creatinine clearance values in healthy males (longitudinal analysis)

Age, years	N	Mean Creatinine clearance (ml/min/1.73m^2)	Creatinine clearance slope (ml/min/1.73m^2/year)
17-24	1	125.3	-1.75
25-34	20	140.4	-1.09
35-44	64	132.7	-0.11
45-54	95	128.1	-0.73

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
55-64	60	121.8		-1.64				
65-74	36	110.0		-1.30				
75-84	17	97.0		-1.07				
Total	293	124.7		-0.90				
In the total healthy male population (N=293), creatinine clearance declined by 0.90 ml/min/1.73m^2/year. The longitudinal data agreed closely with the cross-sectional data, showing a decline in creatinine clearance after age 55. There was NS relationship between BP and creatinine clearance in this healthy population. There was no trend for "first visit artefact" (data not shown). **Note:** limitations: inulin clearance would have been a better measure of renal function, caution in generalising results to females								

Table 299: Ref ID: 3884 [Rule et al. 2004]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rule AD, Gussak HM, Pond GR et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis. 2004; 43(1):112-119. Ref ID: 3884	Cross-sectional Retrospective analysis of medical records USA Evidence level 3	N = 365	**Inclusions:** retrospective review of medical records of potential living kidney donors > 18 years old assessed at the Mayo Clinic between Oct, 1996 to April, 2001. **Exclusion:** history of primary renal or systemic disease, BP > 140/90 mm Hg, fasting serum glucose > 126 mg/dl, urine protein excretion > 150 mg/day, abnormal urine sediment analysis, structural abnormalities (diagnosed by CT urography or angiograghy) **Baseline population:** **N** **365** % Female 56.2 Mean age, years (range) 41.1 (18-71) % living related 71	Objective-to determine normal values for GFR in healthy kidney donors **Protocol:** Data on age, sex, race, body surface area, serum creatinine, and non-radiolabelled iothalamate clearance were obtained from medical records. Serum creatinine was measured by the modified kinetic rate Jaffe on an	GFR measured by non-radiolabelled iothalamate clearance	N/A	Normal values of GFR Change in GFR with increasing age	Not stated

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			donors		autoanalyser. After hydration, 300 mg non-radiolabelled iothalamate was injected subcutaneously and iothalamate was measured in timed plasma and urine samples.				
			% white	80.3					
			% Middle Easterners	3.3					
			% African American	1.4					
			% Hispanic	1.6					
			% Asian/Pacific Islanders	1.4					
			Mean GFR, ml/min/1.73 m^2	101					
			Mean serum creatinine, mg/dl	1.04					

Effect size:

GFR decline

GFR declined with increasing age and this was a steady decline as age increased.

In female healthy kidney donors (N=205), GFR declined by 7.1 ml/min/decade or 0.71 ml/min/year (not normalised to body surface area).

In male healthy kidney donors (N=160), GFR declined by 4.6 ml/min/decade or 0.46 ml/min/year (not normalised to body surface area).

Regression analysis of GFR was significant for age and sex ($p<0.001$ for both).

When normalised to body surface area, GFR declined by 4.9 ml/min/1.73m^2/decade or 0.5 ml/min/1.73m^2/year in the whole sample (N=365).

Regression analysis of GFR normalised surface area was significant for age ($p<0.001$), but not sex ($p=0.826$).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Normal GFR Values by Age								
			GFR, ml/min/1.73m^2 in healthy kidney donors					
Age, years			**5th Percentile**	**Mean**		**95th Percentile**		
20			91	111		136		
30			86	107		131		
40			81	102		126		
50			76	97		121		
60			71	92		116		
65			69	89		113		
70			66	87		111		
75			64	84		109		
Note: Limitations: mostly a white population, 71% of the healthy kidney donors were related to recipients, therefore these donors may have a greater prevalence of subclinical renal disease and the rate of GFR decline could be greater than in the general population.								

Table 300: Ref ID: 3885 [Slack et al. 1976]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Slack TK, Wilson DM. Normal renal function: CIN and CPAH in healthy donors before and after nephrectomy. Mayo Clin Proc. 1976; 51(5):296-300. Ref ID: 3885	Cross-sectional retrospective analysis of medical records Evidence level: 3 I centre Mayo Clinic,USA	N = 141 healthy kidney donors	Inclusion: healthy subjects who had a kidney removed during 1976-1973. Exclusion criteria: to achieve a healthy population for study, subjects with the following diseases were excluded: past history of renal or systemic disease, abnormal physical exam, hypertension, elevated serum creatinine, abnormal urinalysis (> 8 WBC/hpf, > 6 RBC/hpf), urine protein excretion > 300 mg/24-h, abnormal excretory urograms/renal arteriogram Population baseline characteristics: 56% male, no further detail given.	N = 141 Procedure: medical records of healthy subjects who had a nephrectomy were retrospectively reviewed. Records were assessed for measured inulin clearance.	The decline in inulin clearance with increasing age	N/A	Decline in inulin clearance with age	Not stated

Effect size:

Inulin clearance values in healthy kidney donors (cross-sectional data):

Age, years	Mean inulin clearance (ml/min/1.73m^2)	Range, 5th percentile
20	118	90-99
25	115	88-96

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
30		112	86-93					
35		109	84-91					
40		106	82-88					
45		104	80-86					
50		101	78-85					
55		99	75-83					
60		96	73-82					
Inulin clearance decline Inulin clearance declined steadily with increasing age in healthy donors. (mean decline 4 ml/min/decade). There was no tendency for an accelerated decline after the age of 60, although there were few people > 60 years and no data for people > 67 years). There was NS sex differences. **Note:** limitations- retrospective cross-sectional, no information on whether donors were related to people receiving the kidney, thus "healthy" may not be entirely true and these people could have subclinical renal disease (but no information to support or refute this).								

Table 301: Ref ID: 4111 [Wetzels et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wetzels JF, Kiemeney LA, Swinkels DW et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study.[see comment]. Kidney International. 2007; 72(5):632-637. Ref ID: 4111	Cross-sectional study Evidence level: 3 Nijmegen Biomedical Study, Netherlands	N total = 6097 N males = 2823 N females = 3272 N disease-free = 3732 N comorbid conditions = 2365	Inclusion: Nijmegen Biomedical Study: age and sex stratified randomly selected adults (≥ 18 years) living in Nijmegen, Netherlands. Exclusion criteria: not stated Population baseline characteristics: N= 3732 "disease-free" N=1032 hypertension N=358 diabetes N=362 MI N=127 stroke N=145 kidney disease N=347 diuretic/ antihypertensive/ antirheumatic drug use	Age and sex reference values for eGFR N comorbid conditions = 2365 Procedure: People were invited to participate by returning a postal questionnaire on lifestyle and medical history (42% response). Responders donated blood samples for measurement of serum creatinine, which was calibrated to the MDRD laboratory and MDRD eGFR was calculated. No physical exams were carried out and participants were assigned to the comorbid group based on their answers to the question: Have you ever been diagnosed by a physician with MI, stroke or cerebrovascular disease, diabetes, hypertension, or any kidney disease? Specific information of medication use in the last 6 months was gathered.	Age and sex reference values for eGFR N disease-free = 3732	N/A	Age and sex specific eGFR values	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

GFR Decline in healthy people:

GFR decline in healthy people was approximately 0.4 ml/min/year

Age and Gender reference values for eGFR:

Note that a GFR < 60 ml/min/1.73 m2 was within the normal reference range for non-diseased men > 55 years old and non-diseased women > 40 years old. Authors suggest that definition of CKD should be changed . They suggest using a reference-value eGFR below the lower reference threshold.

Estimated GFR in non-diseased Caucasian males of the Nijmegen Biomedical studies

Age (years)	N	Mean +/- SD	Range	P5	P25	P50	P75	P95
18-24	94	100 +/- 13	72-137	77	90	99	109	121
25-29	96	93 +/- 13	67-125	74	82	90	102	117
30-34	118	86 +/-13	63-133	68	77	85	93	107
35-39	125	85 +/-14	61-118	65	74	85	95	110
40-44	143	84 +/- 13	54-124	66	76	83	92	106
45-49	160	83 +/-13	50-123	63	73	82	91	105
50-54	143	79 +/- 12	46-120	60	71	78	87	97
55-59	158	76 +/- 13	27-118	58	68	75	84	98
60-64	149	75 +/- 15	48-199	59	67	73	83	95
65-69	154	75 +/- 14	51-165	56	66	74	82	97
70-74	102	71 +/-12	38-102	54	64	70	79	92
75-79	112	70 +/- 13	41-110	45	62	70	79	91
80-84	73	67 +/- 15	41-129	43	58	69	77	87

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
>85	33	62 +/- 16	34-101	35	47	65	72	92
Values are given as means (s.d.), ranges and 5th, 25th, 50th,75th and 95th percentile **Note:** limitations: questionnaire was used to assess health of participants (no physical exam), so "healthy" people may have actually been diseased; creatinine measured only once; data applies to European Caucasian population								

Q.5.7 Risk factors associated with progression of CKD (2008) (2014 guideline - chapter 7.3)

Table 302: Ref ID: 1086 [Earle 2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Earle KK, Porter KA, Ostberg J et al. Variation in the progression of diabetic nephropathy according to racial origin. Nephrol Dial Transplant. 2001; 16(2):286-290. Ref ID: 1086	Retrospective Case-series Evidence level: 3	N total = 45 N Indo-Asian=10 N African Caribbean=11 N Caucasian = 24 1 centre study: diabetes clinic Whittington Hospital,	**Inclusion:** type 2 diabetic nephropathy (serum creatinine ≥ 170 micromol/l, persistent clinical proteinuria with diabetic retinopathy) **Exclusion criteria:** nondiabetic renal disease, absent retinopathy, congestive cardiac failure and/or malignancy **Population baseline characteristics:** NS difference between Indo-Asians (IA), African-Caribbean (AC) and	N Indo-Asian=10 N African Caribbean=11 **Procedure:** All serum creatinine measurements were identified from medical records. Assignment of racial origin was according to patient's choice on the hospital coding system. Indo-Asian included Indian, Pakistani, or Bangladeshi people. African-Caribbean included	N Caucasian = 24 **Procedure:** As for intervention	Mean 37 months Indo-Asian, mean 46 months African Caribbean, mean 51 months Caucasian	Doubling of serum creatinine Rate of serum creatinine increase (slope=beta)	British Diabetic Association

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		London, UK	Caucasians (C) with respect to follow-up time, diabetes duration, SBP, DBP, smoking, ACE inhibitors usage (90%, 91%, 79% IA, AC, C, respectively), HbA1C, urinary protein excretion, serum creatinine. Indo-Asians were significantly younger (58 years) than AC (68 years) or C (67 years).	Black Caribbean, Black African, Somali or Black other. Caucasian patients were those who selected white. Patients visited the clinic 2-3 times a year and BP, serum creatinine, proteinuria (reagent strip) and 24-h urinary protein excretion were determined.				

Effect size:

Effect of Ethnicity on Doubling of serum creatinine

100% of Indo-Asians experienced a doubling of serum creatinine compared with 45% of African Caribbeans and 50% of Caucasians (p=0.025) during follow-up.

Effect of Ethnicity on Rate of serum creatinine increase

The mean rise in serum creatinine in Indo-Asians (5.36 micromol/l/month) was significantly greater than in African Caribbeans (3.14 micromol/l/month) or Caucasians (2.22 micromol/l/month), p=0.031. This relationship remained after adjustment for DBP.

NS interaction between rate of serum creatinine change and age (p=0.073), treatment regimen (p=0.418), baseline urinary protein excretion (p=0.216), smoking (p=0.118), or gender (p=0.871)

Limitations: small sample size, population was diabetic people with nephropathy

Table 303: Ref ID: 3940 [Elsayed et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Elsayed EF, Tighiouart H, Griffith J et al. Cardiovascular Disease and Subsequent Kidney Disease. Archives of Internal Medicine. 2007; 167(11):1130-1136. Ref ID: 3940	case series Evidence level: 3 USA	N total = 13826 N Subjects with CVD = 1787 N Subjects without CVD = 12039	**Inclusion:** patient data pooled from Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS). ARIC: people 45-64 years old recruited between 1987 and 1989 from 4 communities. CHS: subjects ≥ 65 years old recruited between 1989 and 1990. **Exclusion criteria:** participants with missing data (including baseline or final creatinine measurements), people with baseline GFR < 15 ml/min/1.73 m^2 **Population baseline characteristics:** Mean age 57.6 years. People with baseline CVD were significantly older (60	Subjects with CVD N = 1787 **Procedure:** Baseline serum creatinine measured and calibrated to Third NHANES values. MDRD equation used to estimate GFR. Baseline cardiovascular disease (CVD) defined by stroke, angina, claudication, TIA, coronary angioplasty or bypass, or recognised or silent MI.	Subjects without CVD N = 12039 **Procedure:** As for intervention	Mean 9.3 years. 22% failed to provide last serum creatinine; these people were more likely to have CVD at baseline and had higher CVD risk factors. Authors suggest this exclusion would bias towards null hypothesis.	Kidney function decline (serum creatinine increase of at least 0.4 mg/dl between first and last visit) Kidney function decline (GFR decrease of at least 15 ml/min/1.73 m^2 between first and last visit) Development of CKD (serum creatinine increase of at least 0.4 mg/dl from baseline level of < 1.4 mg/dl in men and < 1.2 mg/dl in women) Development of CKD (GFR decrease	NIH, Amgen, National Heart, Lung, and Blood Institute

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			vs.57 years), had higher prevalence of diabetes and hypertension, and had lower baseline GFR (86 vs.90 ml/min/1.73 m^2) compared to people without CVD at baseline.				of 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2)	

Effect size:

Odds ratios (OR) adjusted for age, sex, race, education, study origin, diabetes, smoking, alcohol use, hypertension history, BMI, SBP, hematocrit, albumin level, HDL cholesterol, total cholesterol, baseline serum creatinine, baseline eGFR.

Effect of Cardiovascular disease on Kidney Function decline (serum creatinine increase of at least 0.4 mg/dl between first and last visit)

After a mean follow-up of 9.3 years, 128 of 1787 (7.2%) people with baseline cardiovascular disease had a decline in kidney function (serum creatinine increase of at least 0.4 mg/dl) compared with 392 of 12039 (3.3%) people without baseline CVD (p<0.001). People with decline in renal function were significantly older, more likely to have hypertension and diabetes, more likely to be African American, and had significantly higher baseline serum creatinine levels than those who did not experience renal function decline.

People with baseline cardiovascular disease (N=1787) had a significantly increased risk of a decline in renal function (serum creatinine increase of at least 0.4 mg/dl) compared with people without CVD at baseline (N=12039) [adjusted OR 1.70 (95% CI 1.36 to 2.13), p<0.001).

Effect of Cardiovascular disease on Kidney Function decline (GFR decrease of at least 15 ml/min/1.73 m^2 between first and last visit)

After a mean follow-up of 9.3 years, 607 of 1787 (34.0%) people with baseline cardiovascular disease had a decline in kidney function (GFR decrease of at least 15 ml/min/1.73 m^2) compared with 3909 of 12039 (32.5%) people without baseline CVD (p=0.22).

People with baseline cardiovascular disease (N=1787) had a significantly increased risk of a decline in renal function (GFR decrease of at least 15 ml/min/1.73 m^2) compared with people without CVD at baseline (N=12039) [adjusted OR 1.28 (95% CI 1.13 to 1.46), p<0.001).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect of Cardiovascular disease on Development of CKD (serum creatinine increase of at least 0.4 mg/dl from baseline level of < 1.4 mg/dl in men and < 1.2 mg/dl in women) People with baseline CVD and baseline serum creatinine < 1.4 mg/dl in men and < 1.2 mg/dl in women had a significantly increased risk of developing CKD (serum creatinine increase of at least 0.4 mg/dl)compared with people without CVD at baseline [adjusted OR 1.75 (95% CI 1.32 to 2.32), p<0.001). **Effect of Cardiovascular disease on Development of CKD** (GFR decrease of at least 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2) People with baseline CVD had an increased risk of developing CKD (GFR decrease of at least 15 ml/min/1.73 m^2 level in people with baseline GFR > 60 ml/min/1.73 m^2) compared with people without baseline CVD [adjusted OR 1.54 (95% CI 1.26 to 1.89), p<0.001). **Sensitivity Analyses:** Similar increased risk when analysis was restricted to ARIC or CHS cohorts separately. Exclusion of people with heart failure: association still remained significant [OR 1.72 (1.12 to 2.62)]. Baseline ACE inhibitors use evaluated: CVD still associated with kidney function decline [OR 1.82 (1.20 to 2.76)] and ACE inhibitors use was protective [OR 0.30 (0.10 to 0.87)]. CVD defined as only MI or cardiac procedure: CVD still associated with decline in kidney function [OR 1.93 (1.45 to 2.59)]. **Limitations:** no baseline proteinuria data, ARIC study had no data on ACE inhibitors use.								

Table 304: Ref ID: 3911 [Evans 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Evans M, Fryzek JP, Elinder CG et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. Am J Kidney Dis. 2005; 46(5):863-870. Ref ID: 3911	case series Evidence level: 3 Sweden	N total = 920	**Inclusion:** Native Swedes age 18-74 years with serum creatinine > 3.5 mg/dl (men) or > 2.8 mg/dl (women) were recruited between May, 1996 and May, 1998. **Exclusion criteria:** participants with serum creatinine elevations due to acute renal failure or dehydration, terminal malignant disease, patients with kidney transplants **Population baseline characteristics:** 65% male, 41% > 65 years old, GFR 1.7 to 14.9 ml/min (33%), GFR 15-19.9 ml/min (59%), GFR 20-23.8 ml/min (7%), diabetic renal disease (31%), glomerulonephritis (24%), nephrosclerosis (15%).	Examining variables associated with progression to RRT in people with Stage 4 and 5 CKD **Procedure:** Patients matching inclusion criteria identified through medical laboratory databases and National Registration Number. Information on anthropometric measurements, lifestyle and medical factors obtained from self-administered mail questionnaires. Medical conditions obtained during routine clinical workup. MDRD equation used to estimate GFR. Patients starting RRT identified from Swedish	N/A **Procedure:** As for intervention	Mean follow-up 2 years (From date of elevated serum creatinine to RRT, death, or Dec., 2002.)	Time to RRT (dialysis or kidney transplantation)	International Epidemiology Institute

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Registry of RRT database.				

Effect size:

Relative risk (RR) adjusted for age, sex, BMI, primary renal disease, and GFR

739/920 (80%) started RRT during follow-up.

Effect of BMI on Progression to RRT:

Compared to people with CKD and BMI 20.1-25 kg/m^2 (N=377), there was NS risk of progression to RRT for people with BMI ≤ 20 kg/m^2 (N=77) [adjusted RR 1.26 (95% CI 0.95 to 1.67)]

Compared to people with CKD and BMI 20.1-25 kg/m^2 (N=377), people with BMI 25.1-30 kg/m^2 (N=314) had a significantly decreased risk of progression to RRT [adjusted RR 0.79 (95% CI 0.67 to 0.94)]

Compared to people with CKD and BMI 20.1-25 kg/m^2 (N=377), there was NS risk of progression to RRT for people with BMI >30 kg/m^2 (N=26) [adjusted RR 0.86 (95% CI 0.68 to 1.07)]

Effect of baseline GFR on Progression to RRT:

People with GFR 16.7-18.4 ml/min had NS risk of progression to RRT compared with people with GFR ≥ 18.5 ml/min [adjusted RR 1.20 (95% CI 0.96 to 1.50)]

People with GFR 13.7-16.6 ml/min had a significantly increased risk of progression to RRT compared with people with GFR ≥ 18.5 ml/min [adjusted RR 1.52 (95% CI 1.21 to 1.91)]

People with GFR < 13.7 ml/min had a significantly increased risk of progression to RRT compared with people with GFR ≥ 18.5 ml/min [adjusted RR 2.27 (95% CI 1.83 to 2.82)]

Age inversely related to risk of RRT, men had more rapid progression than women,

Diabetic nephropathy was associated with a more rapid progression to RRT compared with glomerulonephritis [adjusted RR 1.24 (95% CI 1.02 to 1.51)]

Table 305: Ref ID: 707 [Fored et al. 2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fored CM, Ejerblad E, Lindblad P et al. Acetaminophen, aspirin, and chronic renal failure.[see comment]. New England Journal of Medicine. 2001; 345(25):1801-1808. Ref ID: 707	Case-control study Evidence level: 2 + Sweden	N Cases (patients with chronic renal failure) = 926 N age and sex matched controls = 998	**Inclusion: Cases:** Native Swedes age 18-74 years with serum creatinine > 3.4 mg/dl (men) or > 2.8 mg/dl (women) were recruited between May, 1996 and May, 1998. Controls: Controls were randomly selected from the Swedish Population Register and frequency-matched to cases according to age (10-year age groups) and sex. **Exclusion criteria:** participants with serum creatinine elevations due to acute renal failure, severe heart failure, patients with kidney transplants **Population baseline characteristics:** Overall: 65% male, Mean age 58 years (men), 57 years (women). Median serum creatinine 3.8 mg/dl (male cases) and 3.2 mg/dl (female cases). Median eGFR (MDRD) 22 ml/min (male cases) 19 ml/min (female cases). Among cases: 31% diabetic nephropathy, 24%	Cases (patients with chronic renal failure) N=926 **Procedure:** Laboratory databases searched to identify case patients, and to retrieve clinical and demographic data. Cases and controls completed a self-administered questionnaire and underwent a face-to-face interview (interviewer blinded to study purpose) to assess use of NSAIDs (type, dose, duration of use). Regular use defined as at least 2 tablets/week for two months. Sporadic use defined as a cumulative lifetime dose > 20 tablets but users did	age and sex matched controls N = 998 **Procedure:** As for intervention	N/A	Risk of chronic renal failure (serum creatinine > 3.4 mg/dl (men) or > 2.8 mg/dl (women))	International Epidemiology Institute

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			glomerulonephritis, 15% nephrosclerosis, 10% hereditary renal disease, 10% other renal disease	not use it regularly. Non-users took < 20 tablets during their lifetime.				

Effect size:

Odds ratios (OR) adjusted for age, sex, education, smoking, use or non-use of other analgesics, interaction between aspirin and acetaminophen use.

Acetaminophen not an NSAID.

E**ffect of NSAIDS on risk of chronic renal failure** (CRF- serum creatinine > 3.4 mg/dl (men) or > 2.8 mg/dl (women)

Compared to non-users of aspirin (N cases = 224, N controls= 363) regular users (N cases = 213, N controls= 141) of aspirin had a significantly increased risk of chronic renal failure [adjusted OR 2.5 (95% CI 1.9 to 3.3)]

Compared to non-users of aspirin (N cases = 224, N controls= 363) sporadic users (N cases = 459, N controls= 496) of aspirin had a significantly increased risk of chronic renal failure [adjusted OR 1.5 (95% CI 1.2 to 1.8)]

Compared to non-users of Acetaminophen (N cases = 230, N controls= 376) regular users (N cases = 105, N controls= 71) of Acetaminophen had a significantly increased risk of chronic renal failure [adjusted OR 2.5 (95% CI 1.7 to 3.6)]

Compared to non-users of Acetaminophen (N cases = 230, N controls= 376) sporadic users (N cases = 345, N controls= 413) of Acetaminophen had NS risk of chronic renal failure [adjusted OR 1.3 (95% CI 1.0 to 1.6)]

The risk of CRF increased with increasing cumulative dose of aspirin or acetaminophen. ($p<0.01$ and $p<0.001$ respectively).

An average intake > 500g/year of aspirin significantly increased the risk of CRF [adjusted OR 3.3 (95% CI 1.4 to 8.0)]

Regular use of BOTH aspirin and acetaminophen was associated with a significantly increased risk of CRF compared with regular users of aspirin only [adjusted OR 2.2 (95% CI 1.4 to 3.5)]

Regular use of BOTH aspirin and acetaminophen was NS associated with a risk of CRF compared with regular users of acetaminophen only [adjusted OR 1.6 (95% CI 0.9

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
to 2.7)] NS risk of CRF for other non-aspirin NSAIDs: OR 1.0 Sub-analysis showed regular use of aspirin compared with non-use of aspirin was significantly associated with increased risk of CRF in people with diabetic nephropathy (OR 2.9 (1.9-4.5), glomerulonephritis (OR 2.6 (1.4-4.8), nephrosclerosis (OR 2.1 (1.3-3.5), hereditary renal disease (OR 3.1 (1.6-6.0). **Note:** Interviewers were not blind to who were cases and controls (impossible). Also impossible to rule out bias caused by use of NSAIDs for symptoms of conditions that pre-disposed cases to renal failure.								

Table 306: Ref ID: 558 [Hovind et al. 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hovind P, Rossing P, Tarnow L et al. Smoking and progression of diabetic nephropathy in type 1 diabetes. Diabetes Care. 2003; 26(3):911-916. Ref ID: 558	Prospective cohort Evidence level: 2+	N total = 301 N smokers = 176 N non-smokers = 94 N ex-smokers =31 1 centre study: Steno clinic, Denmark	**Inclusion:** patients with type 1 diabetes and nephropathy (persistent albuminuria > 300 mg/24-h in at least 2 of 3 consecutive 24-h urine collections, presence of diabetic retinopathy) attending the Steno clinic. **Exclusion criteria:** other renal disease **Population baseline characteristics:** NS between groups for duration of diabetes, retinopathy, albuminuria, HbA1C. Ex-smokers (mean 40 years) were significantly older than non-smokers (35 years) or smokers (36 years). Smokers had significantly lower SBP and DBP than non-smokers or ex-smokers. Smokers had significantly higher GFR (92 ml/min/1.73m^2) versus non-smokers (86 ml/min/1.73m^2) or ex-smokers (80	Smokers N = 176 Ex-smokers N=31 **Procedure:** At baseline and every 3-4 months, patients visited the clinic and had BP, blood glucose, HbA1C, albuminuria, weight measured. Patients completed a standardised questionnaire to assess smoking status: Smokers (smoke > 1 cigarette/day during any portion of the study period), ex-smokers (subjects who quit smoking before entering the study and remained non-smokers during the study). GFR was measured annually with ^{51}Cr-EDTA plasma clearance. BP was targeted to < 140/90 mm Hg with antihypertensive therapy with predominantly ACE inhibitors.	Non smokers N = 94 **Procedure:** As for intervention	Median 7 years (range 3-14 years)	decline in GFR	Danish Diabetes Foundation, Hansen Foundation, Per S. Henriksen Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			ml/min/1.73m^2).					
Effect size: Median cigarettes was 20/day in the smokers and had been 20/day in ex-smokers. **Effect of Smoking on GFR** After adjustment for BP, albuminuria, HbA1C and cholesterol, there was NS difference in the rate of GFR decline between non-smokers (mean 4.4 ml/min/year) , ex-smokers (mean 3.4 ml/min/year, and smokers (mean 4.0 ml/min/year). Albuminuria, cholesterol, MAP, and HbA1C were all significant independent predictors of progression.								

Table 307: Ref ID: 290 [Ibanez et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ibanez L, Morlans M, Vidal X et al. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. Kidney International. 2005; 67(6):2393-2398. Ref ID: 290	Case control Evidence level: 2+ Barcelona, Spain	Cases with ESRD = 520 Controls without ESRD = 982	**Inclusion criteria:** Cases: all patients entering dialysis program because of ESRD between June 1995 and Nov. 1997 in all dialysis centres in Barcelona, Spain. Controls: randomly selected from hospital admission lists, including acute conditions not known to be related with NSAID use. **Exclusion criteria**: serious conditions, physical impairment (deafness or blindness), mental disability, illiteracy, renal transplantation recipients, non-residents of Barcelona Population baseline characteristics: Median age 64 years (cases) and 63 years (controls). Cases: glomerulonephritis	Users of analgesics and NSAIDS in Cases with ESRD = 122 Users of analgesics and NSAIDS in controls = 166 **Procedure:** Two controls were age (within 5 years), sex, and hospital matched with each case. Trained nurses interviewed cases and controls about type, dose, and duration of analgesic use, demographics, first diagnosis of renal disease, co-morbid conditions, smoking, alcohol, and caffeine consumption. Investigator abstracted medical records to classify ESRD according to underlying cause of renal disease. Users were people who used any analgesic or NSAID daily or every other day for 30 days	Nonusers of analgesics and NSAIDS in Cases with ESRD = 398 Nonusers of analgesics and NSAIDS in controls = 816	Not applicable	Risk of ESRD	Dept of Health and Social Security

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(17%), vascular nephropathy (34%), interstitial nephritis (13%), diabetic nephropathy (11%), cystic kidney disease (9%), unknown cause (13%)	or longer at any time before the date of the first diagnosis of renal disease. Index date established by 2 independent investigators blinded to drug use from patient and medical record information. Index date for the controls was the same as for the matched cases.				

Effect size:

Odds ratios (OR) adjusted for smoking, hypertension, arteriopathy, diabetes, kidney stones, gout

Effect of Analgesic and NSAID use on Risk for ESRD:

Compared with non-users (N=398 cases, N=816 controls), users of analgesics and NSAIDS (N=122 cases, N=166 controls) had NS risk of ESRD [adjusted OR 1.22 (95% CI 0.89 to 1.66)]

Sub-analysis: Effect of Aspirin use and Risk for ESRD

Users of aspirin (N=81 cases, N=94 controls) had a significantly increased risk of ESRD compared with nonusers [adjusted OR 1.56 (95% CI 1.05 to 2.30)]. The effect of aspirin was related with the cumulative dose (p trend =0.012) and duration of use (p trend= 0.012).

Sub-analysis: Effect of Pyrazolone use and Risk for ESRD

Users of pyrazolones (N=34 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 1.03 (95% CI 0.60 to 1.76)]

Sub-analysis: Effect of non-aspirin NSAID use and Risk for ESRD

Users of non-aspirin NSAIDs (N=37 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 0.94 (95% CI 0.57 to 1.56)]

When the exposure time was increased to 6 months prior to any symptom of renal disease, the OR for ESRD by each drug category was similar.

Smoking and ESRD:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Smokers (N=320 cases, N=557 controls) had a significantly increased risk of ESRD compared with non-smokers [adjusted OR 1.54 (95% CI 1.14 to 2.07)] **Note:** possible recall bias may have caused misclassification of analgesic use.								

Table 308: Ref ID: 2040 [Morlans 1990]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Morlans M, Laporte JR, Vidal X et al. End-stage renal disease and non-narcotic analgesics: A case-control study. British Journal of Clinical Pharmacology. 1990; 30(5):717-723. Ref ID: 2040	Case control Evidence level: 2+ Barcelona, Spain	N Cases with ESRD = 340 N Controls without ESRD = 673	**Inclusion criteria:** Cases: randomly selected (using number tables to recruit at least 50% of each dialysis unit) patients entering dialysis program because of ESRD between 1980 and 1983 in all dialysis centres in Barcelona, Spain. Controls: randomly selected from hospital admission lists, including acute conditions not known to be related with NSAID use. **Exclusion criteria:** serious conditions, physical impairment (deafness or blindness), mental disability, illiteracy, renal transplantation recipients, non-residents of Barcelona. Control exclusions: admissions to obstetrics, radiation therapy, oncology, psychiatry.	Users of analgesics in Cases with ESRD = 70 Users of analgesics in controls = 59 **Procedure:** Two controls were age (within 5 years), sex, and hospital matched with each case. Trained nurses interviewed cases and controls about type, dose, and duration of analgesic use, demographics, first diagnosis of renal disease, co-morbid conditions, smoking, alcohol, and caffeine consumption. Investigator abstracted medical records to classify ESRD according to underlying cause of renal disease. Users were people who used any analgesic or NSAID daily or every other	Nonusers of analgesics Cases with ESRD = 270 Nonusers of analgesics in controls = 614	Not applicable	Risk of ESRD	Dept of Health and Social Security

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Population baseline characteristics: 61% males, NS between cases and controls for smoking and alcohol use	day for 30 days or longer at any time before the date of the first diagnosis of renal disease. Index date of renal disease established by 2 independent investigators blinded to drug use from patient and medical record information. Index date for the controls was the same as for the matched cases.				

Effect size:

Odds ratios (OR) adjusted for recurring headache history, arthritis, kidney stones, hypertension, diabetes

Effect of Overall Analgesic use on Risk for ESRD:

Compared with non-users (N=270 cases, N=614 controls), users of analgesics (N=70 cases, N=59 controls) had a significantly increased risk of ESRD [adjusted OR 2.89 (95% CI 1.78 to 4.68)]

Sub-analysis: Effect of Salicylate use and Risk for ESRD

Users of salicylates (N=23 cases, N=21 controls) had a significantly increased risk of ESRD compared with nonusers [adjusted OR 2.54 (95% CI 1.24 to 5.20)].

Sub-analysis: Effect of Pyrazolone use and Risk for ESRD

Users of pyrazolones (N=15 cases, N=13 controls) had NS risk of ESRD compared with nonusers [adjusted OR 2.16 (95% CI 0.87 to 5.32)]

Sub-analysis: Effect of phenacetin-containing combinations and Risk for ESRD

Users of phenacetin-containing combinations (N=9 cases, N=1 controls) had a significantly increased risk of ESRD compared with nonusers [adjusted OR 19.05 (95% CI 2.31 to 157.4)]

Note: possible recall bias may have caused misclassification of analgesic use.

Table 309: Ref ID: 3964 [Murray et al. 1995]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Murray MD, Black PK, Kuzmik DD et al. Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. American Journal of the Medical Sciences. 1995; 310(5):188-197. Ref ID: 3964	RCT open label Evidence level: 1+ ITT=29 1 centre, Indiana, USA	N total = 29 N patients with renal insufficiency =15 N patients without renal insufficiency =14	**Inclusion:** adults > 65 years with (CrCl < 70 ml/min) or without renal insufficiency (CrCl > 70 ml/min) **Exclusion criteria:** people at risk of nonrenal adverse events from NSAIDS and those with diagnoses that would independently place them at risk of an adverse renal effect of NSAID, people taking glucocorticoids/mineralocorticoids, people who could not tolerate withholding NSAIDs for 2 weeks before the study without causing excess discomfort **Population baseline characteristics:** people with renal insufficiency	N ibuprofen in people with CRI=15 N piroxicam in people with CRI=15 N sulindac in people with CRI=15 Procedure: Participants were recruited from senior citizen centres and assigned to groups with and without renal insufficiency based on the mean of two consecutive 24-h creatinine clearances. Patients in each group were randomly assigned to receive in cross-over fashion 800 mg ibuprofen three times daily, 20 mg piroxicam once daily, and 200 mg sulindac twice daily. Each phase lasted 1 month with a 1 month washout between each phase. Patients permitted acetaminophen and low dose aspirin. Creatinine	N ibuprofen in people without CRI=14 N piroxicam in people without CRI=14 N sulindac in people without CRI=14 Procedure: As for intervention	Not stated (5 months)	Change in creatinine clearance Adverse Events Adverse effects	US Public Health Services Grant, Pfizer

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			were more likely to be male, white, and weigh more than people without renal insufficiency. Mean age 72 (no CRI) and 75 (CRI); CrCl 87 ml/min (no CRI) and 58 ml/min (CRI)	clearance (two 24 hour urine collections) studies performed at baseline and after 1 month of continuous NSAID administration. Vital signs, serum creatinine, electrolytes, adverse events, compliance assessed twice/week.				

Effect size:

Effect of NSAIDS on changes in creatinine clearance

In older people without renal insufficiency (N=14), there were NS changes in creatinine clearance from baseline (before administration of any NSAID) to the last dose (after 1 month of NSAID use) for ibuprofen (1.42 ml/s vs.1.48 ml/s), piroxicam (1.48 ml/s vs.1.46 ml/s) or sulindac (1.46 ml/s vs.1.48 ml/s).

In older people with renal insufficiency (N=15), there were NS changes in creatinine clearance from baseline (before administration of any NSAID) to the last dose (after 1 month of NSAID use) for ibuprofen (1.00 ml/s vs.1.00 ml/s).

In older people with renal insufficiency (N=15), chronic piroxicam use was associated with a significant decrease in creatinine clearance from baseline to 1 month of chronic use (1.12 ml/s vs.1.00 ml/s, 12% decrease, p=0.022).

In older people with renal insufficiency (N=15), chronic sulindac use was associated with a significant decrease in creatinine clearance from baseline to 1 month of chronic use (1.10 ml/s vs.0.98 ml/s, 11% decrease, p=0.022).

NS differences in magnitude of CrCl decrease between piroxicam and sulindac.

Adverse Events:

IN TOTAL: 4 people withdrew due to adverse events: 3 with CRI and 1 without CRI.

1 person without CRI (71 years, 1.46 ml/s baseline CrCl, hypertensive, diabetic, osteoarthritis, obese) and 1 person with CRI (87 years, baseline CrCl 0.76 ml/s, hypertensive, CAD, leg cramps) had an increase in serum creatinine > 40 micromol/l after ibuprofen.

1 patient with CRI (73 years, baseline CrCl 0.86 ml/s, osteoarthritis, hypertension, cerebrovascular and PVD, glaucoma) had to be removed from all three phases as all

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
three drugs produced increases in serum creatinine > 40 micromol/l. 1 patient with CRI had to withdraw due to intolerable epigastric distress, nausea, vomiting. **Adverse Effects:** More common in people with CRI (N=11) than in people without CRI (N=8). Most common complaint was GI discomfort. Edema in 2 patients without CRI (both following piroxicam) **Limitations:** small sample size, but adequately powered to detect changes in renal function (need N=12). Authors suggest monitoring of people with CRI treated with piroxicam or sulindac.								

Table 310: Ref ID: 911 [Orth et al. 1998]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Orth SR, Stockmann A, Conradt C et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney International. 1998; 54(3):926-931. Ref ID: 911	retrospective Case-control Evidence level: 2+	N pairs = 102 N matched IgA-GN pairs = 54 N matched ADPKD pairs = 48 European multi-centre study: Austria, Germany, Italy	**Inclusion:** biopsy-proven IgA-glomerulonephritis (IgA-GN) or ultrasonography-proven autosomal dominant polycystic kidney disease (ADPKD) **Exclusion criteria:** systemic diseases involving the kidney (diabetes, lupus), immunosuppressive therapy, age at renal failure < 21 years **Population baseline characteristics:** NS difference between case (patients with ESRD) and matched controls (renal disease; no ESRD) with respect to age at renal death of cases compared to mean age of controls, age at diagnosis of renal disease, overall antihypertensive medication use, serum cholesterol, low protein diet, lipid lowering medication use. Male cases and controls were similar with	5-15 pack years (cigarettes) N males = 28 males >15 pack years (cigarettes) N males=43 Procedure: Medical records searched to identify case and control patients, and to retrieve clinical and demographic data. Case patients were defined by the presence of ESRD (need for chronic haemodialysis or kidney transplant). Control patients were identified by the failure to progress to serum creatinine value > 3 mg/dl during a minimum observation period of 1 year (with a minimum of 3 creatinine measurements required). Controls did not require RRT. Cases and	0-5 pack years (cigarettes) N males =73 Procedure: As for intervention	N/A Dropouts: 17.9% of controls and 12.2% of cases failed to return smoking questionnaire	ESRD	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			respect to DBP, calcium channel blocker use. SBP was higher in male cases than controls (146 vs.139 mm Hg). ACE inhibitor use was significantly lower in male cases than controls (25% vs.42%). Female cases and controls were similar with respect to SBP and ACE inhibitor use.	controls were matched according to type of renal disease (AKPKD or IgA-GN), gender, region of residence, and age at renal death. Smoking habits were assessed with a standardised mail questionnaire.				

Effect size:

Analysis was restricted to male cases and matched controls (N=72 pairs), as the female pairs (N=30 pairs) were too few. In females, smoking was NS associated with risk of ESRD.

IgA-GN and ADPKD pairs were combined in the analysis as separate analyses showed similar effects of smoking on ESRD

Effect of Smoking on progression to ESRD

CRUDE analysis: Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47), men who smoked 5-15 pack years (N=28 total; N cases = 17, N controls = 11) had a significantly increased odds of ESRD [unadjusted OR 3.5 (95% CI 1.3 to 9.6), p=0.017].

Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47) men who smoked >15 pack years (N=43 total; N cases=29, N controls = 14) had a significantly increased odds of ESRD [unadjusted OR 5.8 (95% CI 2.0 to 17), p=0.001].

There was significant interaction between the smoking variable and ACE inhibitor use (p=0.026). Patients treated with ACE inhibitors (N cases=18, N controls = 30). Patients not treated with ACE inhibitors (N cases = 54, N controls = 42)

Compared to men who did not receive ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and did not receive ACE inhibitors had a significantly increased odds of ESRD [adjusted OR 10.1 (95% CI 2.3 to 45), p=0.002]. adjusted for SBP

Compared to men who received ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and received ACE inhibitors had NS risk of ESRD

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
[adjusted OR 1.4 (95% CI 0.3 to 7.1), p=0.65]. adjusted for SBP **Note:** limitations – females were excluded from analysis due to low frequency of smoking in this group, confounding by other variables?,								

Table 311: Ref ID: 2113 [Orth et al 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Orth SR, Schroeder T, Ritz E et al. Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. Nephrol Dial Transplant. 2005; 20(11):2414-2419. Ref ID: 2113	Prospective cohort Evidence level: 2+	N total = 185 N smokers = 44 N never smokers = 141 1 centre study: Germany	**Inclusion:** patients with type 1 or 2 diabetes attending the clinic **Exclusion criteria:** people with GFR < 60 ml/min/1.73m^2, ex-smokers **Population baseline characteristics:** 60% had type 1 diabetes. 72% non-smokers and 86% smokers had proteinuria > 0.15 g/d. Smokers were significantly younger (47 vs.54 years), more likely to be male, and had a lower GFR than non-smokers (95 vs.107 ml/min). NS difference between smokers and non-smokers with respect to BMI, diabetes type 1, insulin use, duration of diabetes, HbA1c, retinopathy, proteinuria, hypertension, SBP, DBP, ACE inhibitors use, CAD, PVD, stroke.	Smokers N = 44 **Procedure:** At baseline, patients had a physical exam (BP, anthropometry, spot urine test, serum creatinine, cholesterol, triglycerides), an interview, and completed a standardised questionnaire to assess smoking status. GFR was estimated with MDRD equation. Patients had at least 4 annual follow-up visits. Patient management was left to GP in interim.	Never smokers N = 141 Procedure: As for intervention	Median 5.1 years	20% decline in GFR Change in proteinuria	Not stated

Effect size:

BP at baseline was well controlled for both smokers (135/80 mm Hg) and non-smokers (138/79 mm Hg) and improved during follow-up.

Effect of Smoking on GFR

GFR remained stable during follow-up in non-smokers (107 to 106 ml/min) but decreased significantly in smokers (95 to 83 ml/min, p<0.001).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Smokers had a significantly increased odds of a 20% decline in GFR compared to non-smokers [OR 2.52 (95% CI 1.06 to 5.99), p<0.01]. This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACE inhibitors use, BP, proteinuria (F-ratio=65.9, p<0.0001). Male gender and diabetes type independently influenced course of renal function in smokers compared to non-smokers. Male smokers had a significantly increased odds of a 20% decline in GFR compared with male non-smokers [OR 5.32 (95% CI 1.49 to 18.9), p<0.05]. Smokers with type 1 diabetes had a significantly increased odds of a 20% decline in GFR compared with non-smokers with type 1 diabetes [OR 4.49 (95% CI 1.36 to 14.7), p<0.05]. NS for presence or absence of retinopathy, proteinuria, or ACE inhibitors use. **Effect of Smoking on Proteinuria** Proteinuria increased from baseline to the end of the study in smokers (0.36 to 0.44 g/24-h, N=44) and non-smokers (0.47 to 0.54 g/24-h, N=141), but there was NS differences between the two groups.								

Table 312: Ref ID: 3913 [Roderick et al. 1996]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roderick PJ, Raleigh VS, Hallam L et al. The need and demand for renal replacement therapy in ethnic minorities in England. J Epidemiol Community Health. 1996; 50(3):334-339. Ref ID: 3913	Retrospective cross-sectional study Evidence level: 3 53 renal units, England	N RRT patients total = 5901	**Inclusion:** retrospective cross-sectional survey of all English residents > 16 years old accepted for renal replacement therapy (RRT, dialysis or transplantation) in renal units in England in 1991 and 1992. **Exclusion criteria:** Welsh or Scottish residents treated in England, patients returning to dialysis after a failed renal transplant Population baseline characteristics: of 5901 RRT patients, 86.3% were white, 7.7% were Asians, and 4.7% were black people.	Asians on RRT Blacks on RRT **Procedure:** Population denominators for ethnic populations obtained from 1991 census. Underlying disease was specified by renal units using the European Dialysis and Transplant Association coding system. Renal units ascribed patients to Asian (Indian, Pakistani, or Bangladeshi), Black (Black Caribbean, Black African, and Black others) or White ethnicities.	Whites on RRT Procedure: As for intervention	N/A	Acceptance to RRT (dialysis or transplantation)	Dept. of Health

Effect size:

Completeness of the data on RRT acceptances was 99.0% for age, sex, and district of residence, 93.5% for ethnicity, and 91.9% for underlying cause.

1991 Census: 93.8% of English population is white, 3.0% Asian, 1.9% black.

Of 5901 RRT patients, 86.3% were white, 7.7% were Asians, and 4.7% were black people.

Effect of Ethnicity on Acceptance to Renal Replacement Therapy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Asian adults had 3.5 fold higher acceptance rates to RRT compared with white people. Asian men (N=262) had 3.1 fold higher acceptance rates to RRT compared with Caucasian men (N=3063) [RR 3.1, (95% CI 2.7 to 3.5)]. Asian women (N=178) had 3.9 fold higher acceptance rates to RRT compared with Caucasian women (N=1871) [RR 3.9, (95% CI 3.3 to 4.5)]. Black adults had 3.2 fold higher acceptance rates to RRT compared with white people. Black men (N=161) had 3.0 fold higher acceptance rates to RRT compared with Caucasian men (N=3063) [RR 3.0, (95% CI 2.6 to 3.5)]. Black women (N=111) had 3.4 fold higher acceptance rates to RRT compared with Caucasian women (N=1871) [RR 3.4, (95% CI 2.8 to 4.1)]. Acceptance to RRT increased with increasing age, regardless of ethnicity. After standardising rates for age and sex, the relative rate of RRT was 4.2 for Asian people and 3.7 for black people compared to white people. **Underlying Causes of Renal Disease:** Asians [RR 5.5 (95% CI 4.7 to 7.2)] and blacks [RR 6.5 (95% CI 5.1 to 8.3)] had higher rates of RRT compared with white people due to diabetic renal disease. Asians [RR 2.2 (95% CI 1.2 to 4.1)] and blacks [RR 3.2 (95% CI 1.4 to 7.2)] had higher rates of RRT compared with white people due to hypertension. Asians [RR 2.8 (95% CI 1.9 to 4.1)] and blacks [RR 2.3 (95% CI 1.1 to 4.4)] had higher rates of RRT compared with white people due to glomerulonephritis. Asians [RR 5.7 (95% CI 4.5 to 7.2)] and blacks [RR 1.8 (95% CI 1.0 to 3.4)] had higher rates of RRT compared with white people due to “unknown” causes of renal disease. Rates of RRT were still higher in Asians and blacks compared to white people when analysis was restricted to a pooled group of 37 areas with high black and Asian populations (idea is that both whites and ethnic minorities in these areas would have same access to renal services, and the acceptance rates should have therefore been similar among whites ,blacks, and Asians).								

Table 313: Ref ID: 3957 [Xue et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Xue JL, Eggers PW, Agodoa LY et al. Longitudinal study of racial and ethnic differences in developing end-stage renal disease among aged medicare beneficiaries. Journal of the American Society of Nephrology. 2007; 18(4):1299-1306. Ref ID: 3957	Retrospective Case series Evidence level: 3 USA	N total = 1306825 N white =1163868 N black = 94511 N other = 48446	**Inclusion:** 5% random sample of US Medicare beneficiaries > 65 years old followed from Jan. 1, 1993 for up to 10 years or until death. **Exclusion criteria:** ESRD at baseline **Population baseline characteristics:** 89.1% white, 7.2% black. 62% female, mean age 76 years, 16% diabetic, 38% hypertensive	Blacks N=94511 **Procedure:** Data on patients treated for ESRD from USRDS database. Ethnicity (non-Hispanic black or non-Hispanic white) and death data drawn from Denominator Files. Diabetes and hypertension status obtained from Medicare claims.	Whites N=1163868 Procedure: As for intervention	10 years or until death	ESRD	National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Effect size:

After adjustment for age and gender, black people were 2.0 times more likely to have diabetes than white people at baseline and 1.5 times more likely to have diabetes at follow-up. Black people were 2.0 and 1.1 times more likely to have hypertension at baseline and follow-up than white people.

Effect of Ethnicity on ESRD

After adjustment for age and gender, the cumulative 10-year likelihood of developing ESRD was 2.6% in whites and 6.7% in blacks with baseline diabetes. Compared with white people with baseline diabetes (N=175313), black people with baseline diabetes (N=25049) were 2.4 times more likely to develop ESRD.

After adjustment for age and gender, the cumulative 10-year likelihood of developing ESRD was 1.4% in whites and 3.8% in blacks with baseline hypertension.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Compared with white people with baseline hypertension (N=426300), black people with baseline hypertension (N=51016) were 2.5 times more likely to develop ESRD.

After adjustment for age and gender, the cumulative 10-year likelihood of developing ESRD was 0.3% in whites and 1.3% in blacks with no baseline hypertension and no baseline diabetes. Compared with white people with neither baseline hypertension nor diabetes (N=4651490), black people with neither hypertension nor diabetes at baseline (N=34916) were 3.5 times more likely to develop ESRD.

Women had higher risk of ESRD than men: HR adjusted for age

Characteristic	White	Black Men (95% CI)	Black Women (95% CI)
Diabetes baseline	1.0	2.12 (1.90 to 2.36)	2.50 (2.31 to 2.71)
Diabetes follow-up	1.0	1.93 (1.61 to 2.33)	3.41 (2.94 to 3.95)
Hypertension baseline	1.0	2.05 (1.87 to 2.25)	2.82 (2.63 to 3.02)
Hypertension follow-up	1.0	2.22 (1.90 to 2.60)	3.62 (3.17 to 4.13)
No hypertension No diabetes	1.0	3.27 (2.55 to 4.19)	4.03 (2.91 to 5.57)

Limitations: lack of biochemical data, lacks of data on other potential confounders (smoking, socioeconomic status, proteinuria), possible selection bias, caution in extrapolating results to younger people.

Q.5.8 Information, education and support for people with CKD and their carers (2014 guideline – chapter 8.1)

Table 314: Ref ID: 4049 [Manns et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Manns BJ, Taub K, Vanderstrae	RCT Open label	N = 70 1/35 = 3%	**Inclusions:** people with CKD and eGFR < 30 ml/min/1.73 m^2 and	Standard care + 2 phase educational intervention N=35	Standard care (control group)	1 month	Intent to start home-care dialysis	Southern Alberta Renal

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
ten C et al. The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. Kidney International . 2005; 68(4):1777-1783. Ref ID: 4049	Evidence level: 1 + 1 centre, Canada 80% power, blinded, randomised, allotment concealed, not ITT, not	drop-out in control group and 7/35 = 20% drop out in education group	seen at least once in the pre-dialysis renal clinic. **Exclusion**: cognitive dysfunction, non-English-speaking, people who could not do own activities of daily living, currently on dialysis **Baseline population characteristics:** NS differences between groups for age (64.4 years), gender, comorbid conditions (CHF, CHD, PVD, stroke, diabetes), MDRD eGFR (20.4 in education group vs.20.3 ml/min/1.73m^2 in control group, NS)	**Protocol**: Patients were randomised to standard care (teaching about kidney disease, dietary instruction, and different dialysis modalities) or 2 phase education + standard care. The 2-phase education consisted of booklets discussing advantages/disadvantages of self-care dialysis and in depth information on self-care dialysis modalities. A 15 minute video on dialysis modalities was presented. In the second phase, 2 weeks later, a 90 minute group discussion of self-care dialysis consisting of 3-6 patients, a nephrologist, and predialysis nurse was done. A questionnaire assessing intent to start home care dialysis was given at baseline (both groups), at week 2 after the education session (education group only) and at week 4 (both groups)	N=35 **Protocol:** as for intervention			Program, Calgary Health Trust Funds
Effect size **Intention to start self-care dialysis:** At baseline there was NS differences (p=0.6) between the education + standard care group (57.1% intend to start self-care dialysis, N=35) compared with the standard								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

care group (48.6% intend to start self-care dialysis, N=35) for patients' intention to start self-care dialysis.

At study end, significantly more people in the education (post phase 2) + standard care group (82.1% intend to start self-care dialysis, N=28) intended to start self-care dialysis compared with the standard care group (50% intend to start self-care dialysis, N=34) for patients' intention to start self-care dialysis (p=0.015).

There was NS difference (p=0.2) between the education (post phase 1) + standard care group (66.7% intend to start self-care dialysis, N=30) compared with the standard care group at study end (50% intend to start self-care dialysis, N=34) for patients' intention to start self-care dialysis.

Long term follow-up:

Patients followed up for mean 339 days. 10 in total started dialysis: 7 in control and 3 in the intervention group. Importantly, 9/10 patients who started dialysis started the modality they had selected as their planned choice. Thus, the primary outcome was a reliable surrogate marker for the modality eventually selected by the patient. 4/7 controls started self-care dialysis. 2/3 intervention started self-care dialysis.

Note: no blinding, not ITT, underpowered as they needed 30 to 40 people in each arm, and the intervention group only had 28 completing the trial.

Table 315: Ref ID: 4053[Inaguma et al 2006]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Inaguma D, Tatematsu M, Shinjo H et al. Effect of an educational program on the predialysis period for patients with chronic renal failure. Clinical & Experimental Nephrology. 2006; 10(4):274-278. Ref ID: 4053	Retrospective cohort study Evidence level: 2 + 1 centre, Japan	N = 176	**Inclusions:** Retrospective study of people initiating dialysis from 2002-2005 in a renal unit **Exclusion:** rapidly progressive glomerulonephritis, acute renal failure **Baseline population characteristics:** NS differences between groups for age (67 years), gender, cause of CKD, BMI, CrCl (7.3 ml/min in education group vs.6.9 ml/min in no education group, NS). Total protein, albumin, haemoglobin, and hematocrit were significantly higher in the education group than the no education group at start of RRT.	educational intervention N=70 **Protocol:** Patients initiating dialysis were retrospectively reviewed and grouped into those who had received predialysis education and those who did not receive predialysis education. Predialysis education consisted of 4 hours of lectures (10 patients/group) from dieticians, nurses, nephrologists on renal function, chronic renal failure, treatment, daily-life instructions, explanations of different dialysis modalities, dialysis therapy, dietary therapy, medical expense and welfare systems. Those patients who did not receive education did so because dialysis had to be started before the next education program slot or the patient did not want to attend the education course. In this control group, standard dialysis	No educational intervention (control group) N=106 **Protocol:** as for intervention	Retrospective study of people initiating dialysis from 2002-2005	Hospitalisation Planned initiation of RRT (defined as a patient managed by a nephrologist for > 3 months and in whom blood access or a peritoneal catheter had been created or in place 2 weeks before initiation) Emergent initiation of RRT Use of double-lumen catheter for dialysis	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				information was provided by the attending physician if requested by the patient.			Selection of treatment modality	

Effect size:

Planned initiation of RRT

Significantly more people in the predialysis education group (approx 65%, N=70) had a planned initiation of RRT compared with those who did not receive education (approx. 35%, N=106, p=0.001 between groups).

Emergent initiation:

Significantly fewer people in the predialysis education group (approx 35%, N=70) had an emergent (emergency??) initiation of RRT compared with those who did not receive education (approx. 65%, N=106, p=0.001 between groups).

Use of double-lumen catheter for dialysis

Significantly fewer people in the predialysis education group (approx 5%, N=70) used a double-lumen catheter for hemodialysis compared with those who did not receive education (approx. 25%, N=106, p<0.0003 between groups).

Selection of treatment modality:

NS differences between groups for choice of haemodialysis (90% in education group versus 95% in no education group, p=0.126).

NS differences between groups for choice of peritoneal dialysis (10% in education group versus 5% in no education group, p=0.126).

No patient chose to have a renal transplant.

Duration of hospitalisation for purpose of creating an access and starting dialysis:

People who received predialysis education spent significantly fewer days in hospital in the initiation period of RRT (mean 21.2 days, N=70) compared with those who did not receive education (mean 33.3 days, N=106, p=0.001 between groups)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: Bias: due to voluntary participation in education program these patients could have already understood the details of their disease, and could have maintained their health better prior to dialysis initiation than those who did not participate in the education sessions. Retrospective cohort study								

Table 316: Ref ID: 4065 [Levin et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Levin A, Lewis M, Mortiboy P et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. American Journal of Kidney Diseases. 1997; 29(4):533-540. Ref ID: 4065	cohort study Evidence level: 2 + 1 centre, Vancouver, Canada (ignored the Toronto study as irrelevant outcome)	N = 76	**Inclusions:** people initiating dialysis from 1992-1995 in a renal unit at St. Paul's Hospital, Vancouver, Canada. **Exclusion:** changed dialysis modality, failed transplants, unresolved acute renal failure, known to nephrologists < 4 months **Baseline population characteristics:** NS differences between groups for age, proximity to Vancouver, creatinine levels at initiation of dialysis.	Clinic-based education N=37 **Protocol:** Patients entered a predialysis clinic education program or received standard care. The clinic education program consisted of discussions with a nurse educator, physician, social worker, and nutritionist about renal function, BP, bone disease, diet therapy over multiple visits. Frequency of clinic visits and lab tests dictated by severity of renal disease. Mean time spent by patients was 15-33 hours/year of renal insufficiency. Those patients who did not receive clinic-based education were managed according to local practice and seen by nephrologists/GPs for 30-60 min at regular intervals (7-15 hours/year of renal insufficiency). Both groups received educational videos on dialysis modes and demonstrations of the various dialysis modalities.	Standard care (control group) N=39 **Protocol:** as for intervention	initiating dialysis from 1992-1995	Hospitalisation days Urgent dialysis start Percent patients training as outpatients Selection of treatment modality	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size: **Urgent dialysis start:** Significantly fewer people in the clinic-based predialysis education group (13%, N=4/37) required an urgent dialysis start compared with those who received standard care (35%, N=13/39, p<0.05 between groups). **Selection of treatment modality:** NS differences between groups for choice of peritoneal dialysis (53% in clinic-based education group versus 42% in standard care group, p=NS). **Duration of hospitalisation** People who received predialysis education spent significantly fewer days in hospital in the first month of dialysis (mean 6.5 days, N=37) compared with those who received standard care (mean 13.4 days, N=39, p<0.05 between groups) **Percent patients training as outpatients** Significantly more people in the clinic-based predialysis education group (76%, N=37) trained for dialysis as outpatients compared with those who received standard care (43%, N=39, p<0.05 between groups). The clinic-based education group also had better control of MAP, haemoglobin, calcium at initiation of dialysis than those in the standard care group.								

Table 317: Ref ID: 4084 [Lindberg et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lindberg JS, Husserl FE, Ross JL et al. Impact of multidisciplinary, early renal education on vascular access placement. Nephrology News & Issues. 2005; 19(3):35-36. Ref ID: 4084	Retrospective cohort study Evidence level: 2 + 1 centre, USA	N = 147	**Inclusions:** Retrospective study of people with creatinine > 4.0 mg/dl, creatinine clearance < 20 ml/min, albuminuria, or microalbuminuria initiating haemodialysis from 1997-2000 in the Ochsner Clinic Foundation **Exclusion:** previous peritoneal dialysis, previous kidney transplant, pre-existing permanent vascular access. **Baseline population characteristics:** NS differences between groups for age (62 years), race, gender, cause of CKD, albumin, haemoglobin.	Healthy Start Program educational intervention N=61 **Protocol:** Patients were referred to the clinic 6-12 months prior to initiation of dialysis. People in the Healthy Start education program received lectures, handbooks, and slide presentations on renal function, chronic renal failure, treatment, daily-life instructions, explanations of different dialysis modalities, dialysis therapy, and dietary therapy. Those patients who did not receive the Healthy Start education program received care for renal failure inside or outside of the Ochsner clinic (often presenting at the clinic < 30 days before dialysis initiation) and received conventional care (dialysis modality information, CKD video, meeting with a social worker in hospital). Types of vascular access obtained from patient records	No Healthy Start educational intervention (control group) N=86 **Protocol:** as for intervention	Retrospective study of people initiating dialysis from 1997-2000	Vascular Access Placements	Ochsner Clinic Foundation, Amgen, National Nephrology Associates LLC
Effect size:								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Permanent Vascular Access before Initiation of Dialysis:

- Significantly more people in the Healthy Start predialysis education program (77%, N=61) had permanent vascular access placed before initiation of dialysis compared with people who did not participate in the Healthy Start program (36%, N=86, p<0.001 between groups)
- Significantly more people in the Healthy Start predialysis education program (74%, N=61) had arteriovenous fistulas placed before initiation of dialysis compared with people who did not participate in the Healthy Start Clinic program (38%, N=86, p<0.05 between groups). Overall, the Healthy Start education participants had significantly more AVF placed than the non-HSC group (52% HSC versus 10% non-HSC, p<0.001)

Permanent Vascular Access used for dialysis initiation

- Significantly more people in the Healthy Start predialysis education program (49%, N=61) initiated dialysis with a permanent vascular access compared with people who did not participate in the Healthy Start program (23%, N=86, p<0.01 between groups)
- Significantly more people in the Healthy Start predialysis education program (70%, N=61) initiated dialysis with an arteriovenous fistula compared with people who did not participate in the Healthy Start program (30%, N=86, p<0.01 between groups)
- Significantly less people in the Healthy Start predialysis education program (30%, N=61) initiated dialysis with a graft compared with people who did not participate in the Healthy Start program (70%, N=86, p<0.01 between groups)
- Significantly less people in the Healthy Start predialysis education program (51%, N=61) initiated dialysis with a temporary catheter compared with people who did not participate in the Healthy Start program (77%, N=86, p<0.001 between groups).

Q.5.9 Available tools to aid identification and maximise effectiveness of treatment and management of CKD (2014 guideline – chapter 8.2)

Table 318: Ref ID: 4070 [Anandarajah et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Anandarajah S, Tai T, de LS et al. The validity	Cross sectional analysis by	N Stage 3-5 CKD in 1 practice	**Inclusion criteria:** NEOERICA study: medical records of	Aim: to use manual searching to test the validity of computer searching of primary practice	N/A	Not stated	Prevalence of CKD	No funding

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
of searching routinely collected general practice computer data to identify patients with chronic kidney disease (CKD): a manual review of 500 medical records. Nephrol Dial Transplant. 2005; 20(10):2089-2096. Ref ID: 4070	computerised and manual (to validate the computer method) review of medical records Evidence Level: 3 1 primary care practice, UK	identified by computer searching = 492	adults > 18 years old with a valid serum creatinine **Exclusion criteria:** deaths before 2003 **Baseline Characteristics:** not stated	medical records to estimate prevalence of CKD. **Procedure:** MIQUEST computer program used to extract a retrospective dataset of all patients from 1 primary care practice. Records also reviewed manually for additional free text which is not recognised by computerised search. eGFR was calculated with the MDRD equation. Demographic, biochemical data, patient history, examination data, coded diagnoses, and prescription data were collected and cleaned. CKD defined as eGFR < 60 ml/min/1.73 m^2				

Effect size:

Prevalence of CKD:

The study population was standardised to the original study. The adjusted prevalence of Stage 3-5 CKD was 5.1%.

477/492 (97%) were Stage 3; 14/492 (2.8%) were Stage 4, 1/492 (0.2%) was Stage 5.

Only 36/492 (7.3%) of people identified as having stage 3-5 CKD were known to renal services or had a renal diagnosis coded on their records.

Manual checking of medical records:

Identified only 4 additional cases of CKD missed by the computer search. This brought the number of people with a renal disease code or known to renal services to n=40 or 8% (40/492).

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: Limitations –Cross-sectional analysis by retrospectively reviewing medical records. Ethnicity unreliably reported, creatinine not calibrated to original MDRD study, poor recording of proteinuria/haematuria made estimating Stage 1 and 2 difficult.								

Table 319: Ref ID: 4074 [Hemmelgarn et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hemmelgarn BR, Culleton BF, Ghali WA. Derivation and validation of a clinical index for prediction of rapid progression of kidney dysfunction. Qjm. 2007; 100(2):87-92. Ref ID: 4074	Case series (reviewing medical records) Evidence Level: 3 Canada	N total = 10184 N derivation cohort = 6789 N validation cohort = 3395	**Inclusion:** Adults ≥ 66 years with one or more serum creatinine measurements during each of two time periods: July – December, 2001 as well as July – December, 2003. were identified from Calgary Laboratory Services database. **Exclusion criteria:** laboratory measurements associated with a hospital admission, dialysis patients at entry, subjects with more than 12 creatinine measurements in either of the 6 month observation periods, subjects who underwent renal transplant prior to July 1, 2003, subjects with GFR > 90 ml/min/1.73 m^2	Aim: to develop a clinical index tool to identify subjects at risk of rapid progression of kidney disease and to validate this in a separate cohort of older people **Procedure:** eGFR was calculated with the MDRD equation. Serum creatinine measurements were performed in one laboratory. The first serum creatinine measurement (July 1-Dec. 31, 2001) defined the index GFR. Medications dispensed 6 months prior to 2001 index creatinine measurement was used to determine disease categories (cardiac disease, depression, diabetes, hypertension, dyslipidaemia, liver disease, PVD, etc). Disease categories and drug exposures were considered in a stepwise logistic	N/A	2 years	Rapid progression of kidney dysfunction (≥ 25% decline in mean eGFR between the two study periods)	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			Baseline Characteristics: mean age in both validation and derivation cohort was 76.1 years. In the total group, 65% had eGFR 60-89 ml/min/1.73 m^2 and 31% had eGFR 30-59 ml/min/1.73 m^2 and 4% had eGFR < 30 ml/min/1.73 m^2	regression analysis and risk scores were calculated for each subject. The risk scores (from 0 to 4+) were then categorised into risk classes (I to V). Rates of rapid progression were calculated.				

Effect size

Rapid progression of kidney dysfunction (≥ 25% decline in mean eGFR between the two study periods)

Multivariate analysis: Of the 25 disease variables used in the model, only 5 variables were significantly associated with rapid progression of kidney dysfunction:

Age > 75 years [adjusted OR 1.0 (95% CI 1.0 to 1.1)]; point score for risk index = 1

Cardiac disease [adjusted OR 1.5 (95% CI 1.2 to 1.8)]; point score for risk index = 2

Diabetes [adjusted OR 1.9 (95% CI 1.6 to 2.2)]; point score for risk index = 2

Gout [adjusted OR 1.5 (95% CI 1.1 to 2.1)]; point score for risk index = 2

Anti-emetic drug use [adjusted OR 2.9 (95% CI 1.6 to 2.2)]; point score for risk index = 3

Rate of rapid progression of renal dysfunction (%) by risk stratification

Risk index (score)	Derivation cohort N=6789 Rate (%) (95%CI)	Validation cohort N=3395 Rate (%) (95%CI)
Class I (0)	8.6 (7.5 to 9.8)	8.4 (6.8 to 10.1)
Class II (1)	10.9 (9.6 to 12.2)	11.6 (9.8 to 13.5)
Class III (2)	13.9 (11.5 to 16.7)	15.5 (12.1 to 19.5)

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Class IV (3)			15.6 (13.3 to 18.0)		17.3 (13.9 to 21.1)			
Class V (4+)			24.1 (19.9 to 28.8)		21.9 (16.2 to 28.5)			
The rate of rapid progression of kidney dysfunction increased with increasing risk class (see above) in both the derivation and validation cohorts. People in Class V risk index had almost a triple risk of rapid renal disease progression compared with people in the Class 1 risk index. C statistic for the model was 0.59 indicating a modest ability to discriminate between people with and without risk of rapid renal disease progression. **Note:** Limitations – albuminuria was not included in the model, associations not causality, disease categories based on medication use, which may misclassify and underestimate true prevalence of a certain disease, validation of risk scores only done in 1 small cohort								

Table 320: Ref ID: 4134 [Richards et al.2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Richards N, Harris K, Whitfield M, O'Donoghue D, Lewis R, Mansell M et al. The impact of population-based identification of chronic kidney disease using estimated gloerular filtration rate (eGFR) reporting. Nephrology Dialysis and Transplantation. In press 2007. Ref ID: 4134	Longitudinal observational study/before and after Evidence Level: 3 31 practices, Lincolnshire primary care trust , UK	N PCT population = 185434 N eGFR reported in first 12 months of disease management program = 47119	**Inclusion criteria:** Optimal Renal Care UK (ORC UK) study: people > 15 years old identified from automated eGFR reporting from April 1, 2005 to March 31, 2006. **Exclusion criteria:** inpatient blood samples	Aim: to determine if primary practice computerised medical records contain sufficient information to estimate prevalence of CKD. **Procedure:** PCT-based disease management programme (DMP) was guideline and algorithm –based (from draft UK CKD guidelines) for the identification, management, and referral of people with CKD. The DMP used automated eGFR from all routine serum creatinine measures between April 1, 2005 to March 31, 2006 and eGFR was calculated with the MDRD equation. Patients were designated as primary care, secondary care (non-nephrology) or nephrology care depending on the site of origin of the first eGFR received. People with CKD Stage 3-5 originating in either primary or secondary (non-nephrology) were followed up for 12 months, looking for an eGFR originating from within nephrology care. DMP also	N/A	1 year	Prevalence of CKD Nephrology Referral Location of care	Some authors affiliated with Fresenius Medical Care Renal Services UK

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
				comprised community nurses, dieticians and social workers and care was delivered face-to-face and by telephone.				

Effect size

Prevalence of CKD:

- In the first 12 months of the DMP, eGFR was reported in primary care from N=47119 people. eGFR testing increased with increasing age.
- 29% of eGFR results from primary care were consistent with Stage 3-5 CKD, and the estimated prevalence of Stage 3-5 CKD in primary care was 7.3% (5.3% in males and 9.3% in females, p<0.001). The estimated prevalence of Stage 3-5 CKD from all sources was 8.8%.
- 65%, 81% and 49% of people with Stage 3, 4, and 5, respectively, were > 70 years old.

Location of Care:

- 82.6% of people with Stage 3-5 CKD were cared for by primary care. Only 3.7% of people with Stage 3-5 CKD were cared for by nephrology secondary care and 13.7% in non-nephrology secondary care. The majority of people with CKD Stage 5 were cared for by nephrology secondary care, but there were significantly fewer women than men under nephrology care (0.57:1, p<0.001).

Impact of eGFR reporting on nephrology referrals:

- In the year before the DMP, 53 people with Stage 4-5 CKD in the WLPCT were referred to nephrology services and 11 (20.8%) died within 12 months.
- In 2005-2006 (after DMP initiation) the DMP enrolled 483 people with Stage 4 or 5 and N=50 (10.4%) died within 12 months, p<0.05. Suggests that the DMP was having an impact in terms of earlier referral.
- Following initiation of DMP, the number of referrals rose 2.7 times compared to the number of referrals 11 months prior to DMP commencement.
- After introduction of a referral assessment service in October 2005, referrals declined steadily with a reduction of 42% from the peak after 9 months. The referral rate remained 1.5 times greater than before DMP, but the people being referred were more appropriate for nephrology services.
- The referral assessment service showed that 40% of referrals did not follow referral guidelines.
- After initiation of the referral assessment service in the DMP, the referral rate tailed off rapidly and by 6 months a steady state of an average of 5 new CKD stage 4 or

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
5 patients being referred developed. This was a 0.16% incidence and within the capacity of local nephrology services. **Note: Limitations** –some ascertainment bias, unable to ascertain if creatinine was calibrated to MDRD lab in the automated eGFR reporting, creatinine not obtained under fasting conditions, so eGFR could have been underestimated in some people.								

Table 321: Ref ID: 4135 [Richards et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Richards N, Harris K, Whitfield M, O'Donoghue D, Lewis R, Mansell M et al. Primary care-based disease management of chronic disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. Nephrology Dialysis and Transplantation. In press 2007. Ref ID:	Longitudinal observational study/before and after Evidence Level: 3 31 practices, Lincolnshire primary care trust , UK	N total= 483 N stage 3 CKD = 115 N Stage 4 CKD = 297 N Stage 5 CKD = 71	**Inclusion criteria:** Optimal Renal Care UK (ORC UK) study: people > 15 years old identified from automated eGFR reporting from April 1, 2005 to March 31, 2006. **Exclusion criteria:** inpatient blood samples **Baseline characteristics:** Mean age 77.1 years, 47% male, 30% diabetic, 60.4% took statins (declined with decreasing renal function), 52% took ACE or ARB (declined with decreasing renal function)	Before initiation of disease management programme (DMP) **Procedure:** PCT-based disease management programme (DMP) was guideline and algorithm – based (from draft UK CKD guidelines) for the identification, management, and referral of people with CKD. The DMP used automated eGFR from all routine serum creatinine measures between April 1, 2005 to March 31, 2006 and eGFR was calculated with the MDRD equation. People with CKD Stage 4-5 were identified and enrolled in the DMP program consisting of community nurses, dieticians and social workers and care was delivered face-to-face and by telephone. The main goals were patient education, medicine management, dietetic advice, and achieving guideline targets.	After initiation of disease management programme (DMP)	1 year	Achievement of clinical targets Preservation of renal function	Some authors affiliated with Fresenius Medical Care Renal Services UK

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
4135								

Effect size:

Achievement of Clinical Targets:

- In people with Stage 3-5 CKD, the percentage of total cholesterol measurements in target range increased significantly after 9 months of the DMP (64.5% in target at baseline to 75% in target after 9 months, p=0.001).
- In people with Stage 3-5 CKD, there was NS differences in HDL cholesterol, LDL cholesterol, or triglyceride measurements in target range at baseline compared to 9 months on the DMP.
- In people with Stage 3-5 CKD, without diabetes and a PCR < 100, the percentage of SBP measurements in target range increased significantly after 9 months of the DMP (37.1% in target at baseline to 53.2% in target after 9 months, p=0.001).
- In people with Stage 3-5 CKD, without diabetes and a PCR < 100, the percentage of DBP measurements in target range increased significantly after 9 months of the DMP (68.4% in target at baseline to 90.3% in target after 9 months, p=0.01).
- In people with Stage 3-5 CKD, with diabetes or a PCR > 100, there was NS differences in SBP or DBP measurements in target range at baseline compared to 9 months on the DMP.

Preservation of renal function

N=3 people with CKD Stage 3 improved to Stage 2 CKD

N=15 people with Stage 3 CKD deteriorated to Stage 4 CKD

N=113 with Stage 4 CKD improved to Stage 3 CKD

N=1 person with Stage 4 CKD deteriorated to Stage 5

N=4 people with Stage 5 CKD improved to Stage 4

N=8 people with CKD Stage 5 initiated dialysis

N	9 months preceding DMP median fall eGFR (IQR), ml/min/1.73 m^2	12 months after DMP initiation median fall eGFR (IQR), ml/min/1.73 m^2	P value
317	-3.69 (-1.49 to -7.46)	-0.32 (-2.61 to -3.12)	<0.001
122	-9.90 (-6.55 to -12.36)	-1.70 (-6.41 to -1.64)	<0.001

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
(fall eGFR ≥ 5 ml/min/1.73 m^2)								
195 (fall eGFR < 5 ml/min/1.73 m^2)		-1.92 (-0.41 to -3.23)		-0.86 (-1.03 to -3.53)			0.082 NS	
Compared with the 9 preceding months of the DMP the fall in eGFR was significantly less (slower) after 12 months on the DMP. This was also true for people with eGFR fall ≥ 5 ml/min/1.73 m^2 Death was significantly associated with: • Age (RR 1.008, p=0.001) • CKD at presentation (RR 2.538, p=0.026) • SBP < 100 mm Hg (RR 6.128, p=0.035) Composite endpoint (progression to dialysis, death, decline in eGFR≥ 5 ml/min/1.73 m^2) only significantly associated with age (RR 1.063, p=0.005)								

Table 322: Ref ID: 4069 [Stevens et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Stevens PE, O'donoghue DJ, de LS et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results.[see comment]. Kidney International. 2007; 72(1):92-99. Ref ID: 4069	Cross sectional analysis by retrospectively reviewing computerised medical records Evidence Level: 3 17 primary care practices in Kent, Greater Manchester, and West Surrey , UK	N practice population = 162113 N valid creatinine recorded in adults (study cohort) = 38262	**Inclusion criteria**: NEOERICA study: medical records of adults > 18 years old with a valid serum creatinine identified between 1998 to 2003 **Exclusion criteria:** deaths before 2003 **Baseline Characteristics:** of N=38262 people with valid creatinine recorded, mean age was 58 years; female: male was 1.3:1; mean BMI 27.1 kg/m^2, 70% of study population had a creatinine measure in the last 24 months of the five year study period.	**Aim:** to determine if primary practice computerised medical records contain sufficient information to estimate prevalence of CKD. **Procedure:** MIQUEST computer program used to extract a retrospective dataset of all patients from 17 primary care practices. Serum creatinine was calibrated to the method used by the MDRD laboratory and eGFR was calculated with the MDRD equation. Demographic, biochemical data, patient history, examination data, coded diagnoses, and prescription data were collected and cleaned. CKD defined as eGFR < 60 ml/min/1.73 m^2	N/A	5 years	Prevalence of CKD Prevalence of co morbidities (hypertension, CVD, diabetes, anaemia) Achieved BP targets Medication usage	Roche
Effect size:								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Prevalence of CKD:

- Age standardised prevalence of Stage 3-5 CKD was 8.5% and was the prevalence was higher in females (10.6%) than males (5.8%). Serum creatinine calibration increased the proportion of people with Stage 3 CKD by a factor of 1.75 and increased the proportion of people with Stage 4 CKD by a factor of 1.6 (data not shown)
- Numbers of people > 70 years old increased as GFR decreased: 76.7% of people with eGFR < 30 ml/min/1.73 m^2 were > 70 years old. 50% with eGFR 45-59 ml/min/1.73 m^2 were > 70 years old.
- Of the study cohort (N=38262), 11731(30.7%) had an eGFR < 60 ml/min/1.73 m^2. However, only 242 (2.1%) of these were coded as a renal diagnosis in the records. The recording of a renal diagnosis improved as renal function declined: 19.2% had a recorded renal diagnosis in people with eGFR < 30 ml/min/1.73 m^2

Anaemia:

Records showed that 84.6% of the cohort (32385/38262) had concurrent haemoglobin levels tested.

Anemia (WHO definition, KDOQI definition, or Hb < 11 g/dl) increased with decreasing eGFR.

Hypertension:

21332/38262 (55.8%) were recorded as hypertensive (code or BP > 140/90 mm Hg). Hypertension increased with declining eGFR.

ACE/ARB use was overall 33.2% in people with hypertension and use fell as eGFR declined: 43% used ACE/ARB with eGFR 45-59 ml/min/1.73 m^2 whereas 32.5% used ACE/ARB with eGFR < 30 ml/min/1.73 m^2

BP targets:

BP targets were not achieved in most instances: only 63/461 (13.7%) of people with hypertension and eGFR < 30 ml/min/1.73 m^2 achieved BP < 130/80 mm Hg. Only 571/6235 (9.2%) people with hypertension and eGFR 45-59 ml/min/1.73 m^2 achieved BP < 130/80 mm Hg.

Diabetes:

4063/38262 (10.6%) had a recorded diagnosis of diabetes. Diabetes prevalence increased as GFR decreased. In those with diabetes and eGFR < 60 ml/min/1.73 m^2, ACE/ARBS were prescribed in 690/1601 (44%), aspirin and/or antiplatelet drugs in 621/1601 (39.6%), and lipid lowering agents in 942/1601 (60.1%). Only 270/1313 (20%) with diabetes, hypertension, and eGFR < 60 ml/min/1.73 m^2 achieved target BP < 130/80 mm Hg.

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
CVD: 7620/38262 (20%) had CVD and CVD prevalence increased as eGFR decreased. 50% of people with eGFR < 30 ml/min/1.73 m^2 had CVD and 27% of people with eGFR 45-59 ml/min/1.73 m^2 had CVD. 41% of people CVD and with eGFR < 60 ml/min/1.73 m^2 took ACE/ARBS compared with 34% of people with CVD and eGFR > 60 ml/min/1.73 m^2 (p<0.001) **Note:** Limitations –Cross-sectional analysis by retrospectively reviewing medical records. Ethnicity unreliably reported, neyman bias, poor recording of proteinuria/haematuria made estimating Stage 1 and 2 difficult.								

Table 323: Ref ID: 4110 [Weiner et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Weiner DE, Tighiouart H, Elsayed EF et al. The Framingham predictive instrument in chronic kidney disease. Journal of the American College of Cardiology. 2007; 50(3):217-224. Ref ID: 4110	Observational study Evidence level: 3 USA	N Framingham derivation cohort= 5251 N Subjects with CKD = 934	**Inclusion:** patient data pooled from Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS). ARIC: people 45-64 years old recruited between 1987 and 1989 from 4 communities. CHS: subjects ≥ 65 years old recruited between 1989 and 1990. **Exclusion criteria:** people > 74 years old, people with baseline GFR < 15 ml/min/1.73 m^2, people with missing baseline coronary heart disease status or missing laboratory data **Population baseline characteristics:** Compared with the Framingham derivation cohort, people with CKD were older (65 years CKD vs.48 years Framingham), more likely to have diabetes (14% CKD vs.5% Framingham) and more likely to have optimal BP in the range of SBP < 120 mm Hg, DBP < 80 mm Hg (25% CKD vs.20% Framingham). Mean eGFR of CKD cohort was 52.9 ml/min/1.73	Subjects with CKD (from the pooled ARIC and CHS studies) N = 934 **Procedure:** Baseline serum creatinine measured and calibrated to Third NHANES values. MDRD equation used to estimate GFR. Framingham risk scores calculated for each individual with CKD to derive the 5 and 10 year Framingham probability of a coronary event.	Framingham cohort N = 5251 **Procedure:** As for intervention	N/A	Ability of the Framingham prediction model to predict 5 year and 10 years risk of cardiac events (Myocardial infarction (MI) and Fatal coronary heart disease) in people with CKD	National Heart, Lung, and Blood Institute, Amgen

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			m^2					

Effect size

Among men with CKD (N=357), there were 35 (9.8%) cardiac events within 5 years and 74 (20.7%) cardiac events within 10 years. 53 (14.8%) men with CKD died within 5 years and 126 (35.3%) men with CKD died within 10 years.

Among women with CKD (N=577) there were 30 (5.2%) cardiac events within 5 years and 56 (9.7%) cardiac events within 10 years. 54 (9.4%) women with CKD died within 5 years and 120 (20.8%) women with CKD died within 10 years.

Best Cox regression coefficients for people with CKD and for the original Framingham cohorts for 10-year cardiac outcomes:

Note that Best cox models use the same traditional risk factors as the original Framingham equation, but assign different weight to each factor

For men, beta coefficients were significantly different for men with CKD compared with men in the original Framingham cohort for both the hyperlipidaemia group (beta = - 0.37 CKD versus beta = + 0.74 Framingham, $p<0.05$) and the Stage 2-4 hypertension group (beta = -0.05 CKD versus beta = + 0.90 Framingham, $p<0.05$)

For women, beta coefficients were significantly different for women with CKD compared with women in the original Framingham cohort for both the high normal hypertension group (beta = + 1.07 CKD versus beta = - 0.37 Framingham, $p<0.05$) and the Stage 2-4 hypertension group (beta = +2.24 CKD versus beta = + 0.61 Framingham, $p<0.05$)

Discrimination (the ability of the Framingham prediction model to separate those who had cardiac events from those who did not; quantified by the C-statistic which is analogous to area under the receiver operating characteristic curve)

The Framingham prediction equation had poor discrimination in the CKD cohort. Framingham equation correctly identified males with CKD who would develop a cardiac event within 10 years only 60% of the time, compared with 69% of the time in the non-CKD male cohort and 73% in the original Framingham cohort.

Best cox models significantly improved discrimination.

In women with CKD, discrimination was 73% for 10-year cardiac events compared with 76% in the original Framingham cohort.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Calibration (assesses whether predicted outcomes and actual outcomes agree and is quantified with the chi-square statistic, with high chi square values indicating poor calibration): Among men with CKD, the Framingham equation under predicted cardiac events when people were stratified into quintiles of Framingham Risk.. The 5 -year calibration for men was poor (chi-square 33.4, p<0.001) and the 10 year calibration was also poor (chi-square 71.3, p<0.001). Similarly, the Framingham equation under predicted cardiac events in women with CKD, resulting with poor 5 year (chi square 61.2, p<0.01) and 10 year (chi square 75.1, p<0.01) calibration. Re-calibrated models performed better, although prediction remained poor in men with CKD (5 year chi square 13.7, p=0.01 and 10 year chi square 32.3, p<0.01). In women with CKD, re-calibration showed NS difference in predicted and observed cardiac events in 5 and 10 year probability models. Sensitivity Analyses: Calibration of the Framingham equation for composite outcome of MI and all-cause mortality showed that the event rate increased as Framingham risk rose. Best cox models performed well for 5 and 10 year probabilities in men and women. Authors conclude that Framingham equations do not accurately predict cardiac events in people with CKD. **Limitations:** no baseline proteinuria data, CKD population had moderate CKD and thus no information on how Framingham equation predicts cardiac events in people with more advanced CKD								

Q.5.10 Lifestyle modification (2014 guideline – chapter 8.3)

Table 324: Ref ID: 414 [Castaneda et al.2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Castaneda C, Gordon PL, Uhlin KL et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial.[see comment]. Annals of Internal Medicine. 2001;	RCT Evidence level: 1+ Randomised, blinded 1 centre USA Not ITT	N =26 Drop out rate 0% in each arm	**Inclusion criteria:** people > 50 years with CKD (creatinine 133-442 micromol/l or 1.5-5.0 mg/dl) **Exclusion criteria:** MI in past 6 months, unstable chronic condition, dementia, alcoholism, dialysis or RRT, current resistance training, recent involuntary weight change (2 kg), albumin < 30 g/l, proteinuria > 10 g/d, abnormal stress test result at screening **Baseline characteristics:** NS differences between people randomised to resistance training or	N=14 Resistance training + low protein diet **Procedure:** Nutrition status and adherence to low-protein diet (0.6 g/kg body weight per day) was observed for 2-8 weeks run-in. Participants randomised to resistance group + low protein diet (three exercise sessions/week supervised by a blinded trainer with increasing workloads on five weight resistance machines) or to sham training + low protein diet (gentle movements of upper and lower body while standing, sitting and bending designed to have no physiologic impact). Muscle strength tests determined at baseline and after 12 weeks of	N=12 Sham training + low protein diet	3 months	Change in muscle strength Change in GFR Total body K	National Institute on Aging, New England Medical Center Research Fund, US Dept. of Agriculture Research Service

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
135(11):965-976. Ref ID: 414			sham training for gender, age (65 years), GFR (24 or 27 ml/min), body composition, biochemical or health variables	training. GFR (^{125}I-iothalamate), biochemical measures determined at baseline and 12 weeks after randomisation.				

Effect size:

Adherence to resistance training was 91% and to sham training was 90%. NS difference.

Adherence to low protein diet: resistance training group consumed 108% of target protein levels and sham group consumed 112% of target protein levels (NS between groups)

Change in muscle strength: People who took resistance training + low protein diet had an increase in muscle strength (+32%, N=14), whereas the sham training + low protein diet had decreased overall muscle strength (-13%, N=12). P<0.001 between groups.

Change in Total body Potassium: Resistance training increased total body potassium in the resistance training + low protein diet (+4%, N=12), whereas potassium decreased in the sham training + low protein diet (-6%, N=11), p=0.014 between groups

Change in GFR: GFR increased in people with resistance training + low protein diet (+ 1.18 ml/min/1.73m^2 absolute change, N=14), whereas GFR decreased in the sham training + low protein diet group (-1.62 ml/min/1.73m^2 absolute change, N=12). P=0.048 between groups.

No exercise adverse events or injuries were reported in either group.

Assessment of bias: small study may not be adequately powered to detect changes between groups.

Table 325: Ref ID: 4016 [Eidemak et al. 1997]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Eidemak I, Haaber AB, Feldt RB et al. Exercise training and the progression of chronic renal failure.[see comment]. Nephron. 1997; 75(1):36-40. Ref ID: 4016	RCT Evidence level: 1+ Randomised, blinding not applicable Denmark ITT	N =30 Drop out rate 20% in exercise 26% in usual	**Inclusion criteria:** nondiabetic people with moderate progressive CKD (median GFR 25 ml/min/1.73m^2, range 10-43 ml/min/1.73m^2) **Exclusion criteria:** not stated **Baseline characteristics:** NS differences between people randomised to exercise training or control (usual, sedentary lifestyle) for gender, age (45 years), GFR (26 ml/min) aerobic work capacity, BP, progression of nephropathy (reciprocal of serum creatinine vs.time)	N=15 Exercise training **Procedure:** Patients randomised to exercise group (mainly bicycle ergometer exercise in the patient's home, running, swimming, and walking) or to control group (patients maintained their usual, mostly sedentary lifestyle). Exercise duration and intensity gradually increased up to 60-75% of maximal exercise capacity determined by exercise testing. Exercise tests were performed before randomisation and at the end of the study. Exercise testing consisted of cycling on an electronically braked bicycle ergometer coupled to a cardiopulmonary gas exchange system. Plasma creatinine, physical exam, and clinical chemistry tests performed at baseline and every month. GFR	N=15 Usual (sedentary lifestyle)	1.5 years or until death or RRT (median 20 months in control and 18 months in the exercise group	Change in maximal aerobic work capacity Progression of renal disease (slope of GFR vs.time) Blood lipids (triglycerides, VLDL, LDL, HDL cholesterol, total cholesterol)	University of Copenhagen, Medical Foundation if Greater Copenhagen, Danish Kidney Foundation, Novo Foundation, Faroe Islands and Greenland, Lilly Bertine Lund's Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				(^{51}Cr-EDTA clearance) was measured at baseline, and every 3-9 months.				

Effect size:

3 people in the exercise group started dialysis, N=2 in the control group started dialysis.

N=1 control died (unknown reason)

N=1 control withdrew after 10 months for personal reasons.

Change in maximal aerobic work capacity: Maximal aerobic work capacity significantly increased in the exercise group (N=15; 25 ml O_2/ (min X kg BW) at baseline to 27 ml O_2/ (min X kg BW) after 18 months, $p<0.05$), whereas maximal aerobic work capacity did NS change in the control group (N=15, 21 ml O_2/ (min X kg BW) at baseline to 19 ml O_2/ (min X kg BW) after 20 months, p NS).

Change in GFR: Median GFR decreased in both control (N=15; -0.28 ml/min/month) and exercise groups (N=15; -0.27 ml/min/month, NS between treatments)

Blood Lipids: NS changes from baseline in triglycerides, VLDL, HDL, LDL cholesterols in exercise or control groups. Total cholesterol significantly increased from baseline in the exercise group, $p<0.05$. NS changes from baseline for total cholesterol in the control group.

Assessment of bias: No blinding (not possible), small study N=15 in each arm may not be adequately powered to detect changes between groups. Authors note that renal function did not decline with exercise and suggest that exercise is neither detrimental nor overly beneficial to this population. Exercise could have other benefits (cardiovascular, feelings of well-being, etc)

Table 326: Ref ID: 558 [Hovind et al. 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hovind P, Rossing P, Tarnow L et al. Smoking and progression of diabetic nephropathy in type 1 diabetes. Diabetes Care. 2003; 26(3):911-916. Ref ID: 558	Prospective cohort Evidence level: 2 +	N total = 301 N smokers = 176 N non-smokers = 94 N ex-smokers =31 1 centre study: Steno clinic, Denmark	**Inclusion:** patients with type 1 diabetes and nephropathy (persistent albuminuria > 300 mg/24-h in at least 2 of 3 consecutive 24-h urine collections, presence of diabetic retinopathy) attending the Steno clinic. **Exclusion criteria:** other renal disease **Population baseline characteristics:** NS between groups for duration of diabetes, retinopathy, albuminuria, HbA1C. Ex-smokers (mean 40 years) were significantly older than non-smokers (35 years) or smokers (36 years). Smokers had significantly lower SBP and DBP than non-smokers or ex-smokers. Smokers had significantly higher GFR (92 ml/min/1.73m^2) versus non-smokers (86 ml/min/1.73m^2) or ex-smokers (80 ml/min/1.73m^2).	Smokers N = 176 Ex-smokers N=31 **Procedure:** At baseline and every 3-4 months, patients visited the clinic and had BP, blood glucose, HbA1C, albuminuria, weight measured. Patients completed a standardised questionnaire to assess smoking status: Smokers (smoke > 1 cigarette/day during any portion of the study period), ex-smokers (subjects who quit smoking before entering the study and remained non-smokers during the study). GFR was measured annually with ^{51}Cr-EDTA plasma clearance. BP was targeted to < 140/90 mm Hg with antihypertensive therapy with predominantly ACE inhibitors.	Non smokers N = 94 **Procedure:** As for intervention	Median 7 years (range 3-14 years)	decline in GFR	Danish Diabetes Foundation, Hansen Foundation, Per S. Henriksen Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size: Median cigarettes was 20/day in the smokers and had been 20/day in ex-smokers. **Effect of Smoking on GFR:** After adjustment for BP, albuminuria, HbA1C and cholesterol, there was NS difference in the rate of GFR decline between non-smokers (mean 4.4 ml/min/year) , ex-smokers (mean 3.4 ml/min/year, and smokers (mean 4.0 ml/min/year). Albuminuria, cholesterol, MAP, and HbA1C were all significant independent predictors of progression.								

Table 327: Ref ID: 290 [Ibanez, 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ibanez L, Morlans M, Vidal X et al. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. Kidney International. 2005; 67(6):2393-2398. Ref ID: 290	Case control Evidence level: 2+ Barcelona, Spain	Cases with ESRD = 520 Controls without ESRD = 982	**Inclusion criteria:** Cases: all patients entering dialysis program because of ESRD between June 1995 and Nov. 1997 in all dialysis centers in Barcelona, Spain. Controls: randomly selected from hospital admission lists, including acute conditions not known to be related with NSAID use. **Exclusion criteria:** serious conditions, physical impairment (deafness or blindness), mental disability, illiteracy, renal transplantation recipients, non-residents of Barcelona **Population baseline characteristics:**Median age 64 years (cases) and 63 years (controls). Cases: glomerulonephritis (17%),	Users of analgesics and NSAIDS in Cases with ESRD = 122 Users of analgesics and NSAIDS in controls = 166 **Procedure:** Two controls were age (within 5 years), sex, and hospital matched with each case. Trained nurses interviewed cases and controls about type, dose, and duration of analgesic use, demographics, first diagnosis of renal disease, co-morbid conditions, smoking, alcohol, and caffeine consumption. Investigator abstracted medical records to classify ESRD according to underlying cause of renal disease. Users were people who used any analgesic or NSAID daily or every other day for 30 days or longer at any time before the date of the first diagnosis of renal disease. Index date established by 2 independent investigators	Nonusers of analgesics and NSAIDS in Cases with ESRD = 398 Nonusers of analgesics and NSAIDS in controls = 816	Not applicable	Risk of ESRD	Dept of Health and Social Security

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			vascular nephropathy (34%), interstitial nephritis (13%), diabetic nephropathy (11%), cystic kidney disease (9%), unknown cause (13%)	blinded to drug use from patient and medical record information. Index date for the controls was the same as for the matched cases.				

Effect size:

Odds ratios (OR) adjusted for smoking, hypertension, arteriopathy, diabetes, kidney stones, gout

Effect of Analgesic and NSAID use on Risk for ESRD: Compared with non-users (N=398 cases, N=816 controls), users of analgesics and NSAIDS (N=122 cases, N=166 controls) had NS risk of ESRD [adjusted OR 1.22 (95% CI 0.89 to 1.66)]

Sub-analysis: Effect of Aspirin use and Risk for ESRD: Users of aspirin (N=81 cases, N=94 controls) had a significantly increased risk of ESRD compared with nonusers [adjusted OR 1.56 (95% CI 1.05 to 2.30)]. The effect of aspirin was related with the cumulative dose (p trend =0.012) and duration of use (p trend= 0.012).

Sub-analysis: Effect of Pyrazolone use and Risk for ESRD: Users of pyrazolones (N=34 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 1.03 (95% CI 0.60 to 1.76)]

Sub-analysis: Effect of non-aspirin NSAID use and Risk for ESRD: Users of non-aspirin NSAIDs (N=37 cases, N=51 controls) had NS risk of ESRD compared with nonusers [adjusted OR 0.94 (95% CI 0.57 to 1.56)]

When the exposure time was increased to 6 months prior to any symptom of renal disease, the OR for ESRD by each drug category was similar.

Smoking and ESRD: Smokers (N=320 cases, N=557 controls) had a significantly increased risk of ESRD compared with non-smokers [adjusted OR 1.54 (95% CI 1.14 to 2.07)]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: possible recall bias may have caused misclassification of analgesic use.								

Table 328: Ref ID: 318 [Morales 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Morales E, Valero MA, Leon M et al. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. American Journal of Kidney Diseases. 2003; 41(2):319-327. Ref ID: 318	RCT Evidence level: 1+ Not blinded Spain	N =30	Inclusion criteria: chronic (> 1 year duration) proteinuric (> 1 g/24-h urine protein on at least 3 consecutive determinations in preceding 6 months) nephropathy of diabetic or nondiabetic origin , BMI > 27 kg/m^2) Exclusion criteria: Unstable renal disease, nephrotic syndrome requiring diuretic therapy, immunosuppressive therapy, hypertension requiring > 2 antihypertensive agents	Low calorie diet N=20 Procedure: Prior to the study, all patients completed a 2 month observation period with a full history, exam, blood pressure, BMI, and lab tests. ACE inhibitors, nondihydropyridine CCBs, and ARBs were withdrawn 6 weeks prior to randomisation. Statins and antihypertensive agents (other than ACE, ARB, or CCB) permitted as long as dose remained the same throughout. BP targeted to < 140/90 mm Hg (doxazosin as first choice, then amlodipine if needed) Patients randomised 2:1 to low-calorie normo-protein diet group or control (usual diet) group. The low-calorie normo-protein diet was a reduction of 500 kcal with respect to the individual's usual diet (determined from 3 day food diaries) and consisted of 25-30% fat and 55-65% carbohydrate of totl caloric intake. Protein content was adjusted to 1 to	Usual diet N=10	5 months	BMI Change in protein excretion Change in CrCl Change in serum creatinine	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Baseline characteristics: NS differences between people randomised to low calorie or usual diet	1.2 g/kg/day. Physical exam, BMI, BP, weight, interview with dietician performed at baseline and weeks 1,3, and 5 after randomisation. Laboratory evaluations performed at baseline, 1 and 5 months later. CrCl estimated from Cockcroft Gault.				

Effect size:

Weight: Weight significantly decreased after 5 months of a low calorie diet (87.5 kg at baseline to 83.9 kg after 5 months, $p<0.01$, N=20), whereas weight increased significantly in the usual diet group (96.1 kg at baseline to 98 kg at 5 months, $p<0.05$, N=10) and $p<0.05$ between groups.

BMI: BMI significantly decreased after 5 months of a low calorie diet (33 kg/m^2 at baseline to 31.6 kg/m^2 after 5 months, $p<0.01$, N=20) and significantly increased in the usual diet group (34.3 kg/m^2 at baseline to 35 kg/m^2 after 5 months, $p<0.05$, N=10) and $p<0.05$ between groups.

BP: NS changes in SBP and DBP in either low calorie or usual diet groups.

Change in CrCl: There were NS changes in CrCl after 5 months of low calorie diet, however CrCl significantly decreased in the usual diet group (61.8 ml/min/1.73 m^2 at baseline to 56 ml/min/1.73 m^2 after 5 months, $p<0.05$) NS changes between groups

Change in serum creatinine: There were NS changes in serum creatinine after 5 months of a low calorie diet, whereas creatinine significantly increased after 5 months of a usual diet (1.6 mg/dl at baseline to 1.8 mg/dl at 5 months, $p<0.05$) NS between groups.

Change in protein excretion: Urinary protein excretion significantly decreased after 5 months of a low calorie diet (2.8 g/24-h at baseline to 1.9 g/24-h at 5 months, -31% reduction, $p<0.05$). There was a NS increase in proteinuria in the usual diet group (3 g/24-h at baseline to 3.5 g/24-h at 5 months, NS). ($p<0.05$ between groups).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Weight loss was significantly correlated with a decrease in UPE (r=0.62, p<0.01), but not BP or creatinine clearance. Results were similar when diabetic and nondiabetic people were analysed separately. **Assessment of bias:** small study N=30 and short follow-up (5 months) No blinding, Cockcroft Gault less accurate to estimate CrCl in obese people.								

Table 329: Ref ID: 911 [Orth et al. 1998]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Orth SR, Stockmann A, Conradt C et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney International. 1998; 54(3):926-931. Ref ID: 911	retrospective Case-control Evidence level: 2 +	N pairs = 102 N matched IgA-GN pairs = 54 N matched ADPKD pairs = 48 European multi-centre study: Austria, Germany, Italy	**Inclusion:** biopsy-proven IgA-glomerulonephritis (IgA-GN) or ultrasonography-proven autosomal dominant polycystic kidney disease (ADPKD) **Exclusion criteria:** systemic diseases involving the kidney (diabetes, lupus), immunosuppressive therapy, age at renal failure < 21 years **Population baseline characteristics:** NS difference between case (patients with ESRD) and matched controls (renal disease; no ESRD) with respect to age at renal death of cases compared to mean age of controls, age at diagnosis of renal disease, overall antihypertensive medication use, serum cholesterol, low protein diet, lipid lowering medication use. Male cases and controls were similar with	5-15 pack years (cigarettes) N males = 28 males >15 pack years (cigarettes) N males=43 **Procedure:** Medical records searched to identify case and control patients, and to retrieve clinical and demographic data. Case patients were defined by the presence of ESRD (need for chronic haemodialysis or kidney transplant). Control patients were identified by the failure to progress to serum creatinine value > 3 mg/dl during a minimum observation period of 1 year (with a minimum of 3 creatinine measurements required). Controls did not require RRT. Cases and	0-5 pack years (cigarettes) N males =73 **Procedure:** As for intervention	N/A Dropouts: 17.9% of controls and 12.2% of cases failed to return smoking questionnaire	ESRD	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			respect to DBP, calcium channel blocker use. SBP was higher in male cases than controls (146 vs.139 mm Hg). ACE inhibitor use was significantly lower in male cases than controls (25% vs.42%). Female cases and controls were similar with respect to SBP and ACE inhibitor use.	controls were matched according to type of renal disease (AKPKD or IgA-GN), gender, region of residence, and age at renal death. Smoking habits were assessed with a standardised mail questionnaire.				

Effect size:

Analysis was restricted to male cases and matched controls (N=72 pairs), as the female pairs (N=30 pairs) were too few. In females, smoking was NS associated with risk of ESRD.

IgA-GN and ADPKD pairs were combined in the analysis as separate analyses showed similar effects of smoking on ESRD

Effect of Smoking on progression to ESRD: CRUDE analysis: Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47), men who smoked 5-15 pack years (N=28 total; N cases = 17, N controls = 11) had a significantly increased odds of ESRD [unadjusted OR 3.5 (95% CI 1.3 to 9.6), p=0.017].

Compared to men who smoked for 0-5 pack-years (N=73 total; N cases=26, N controls=47) men who smoked >15 pack years (N=43 total; N cases=29, N controls = 14) had a significantly increased odds of ESRD [unadjusted OR 5.8 (95% CI 2.0 to 17), p=0.001].

There was significant interaction between the smoking variable and ACE inhibitor use (p=0.026). Patients treated with ACE inhibitors (N cases=18, N controls = 30). Patients not treated with ACE inhibitors (N cases = 54, N controls = 42)

Compared to men who did not receive ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and did not receive ACE inhibitors had a significantly increased odds of ESRD [adjusted OR 10.1 (95% CI 2.3 to 45), p=0.002]. adjusted for SBP

Compared to men who received ACE inhibitors and smoked for 0-5 pack-years, men who smoked > 5 pack years and received ACE inhibitors had NS risk of ESRD

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
[adjusted OR 1.4 (95% CI 0.3 to 7.1), p=0.65]. adjusted for SBP **Note:** limitations – females were excluded from analysis due to low frequency of smoking in this group, confounding by other variables?,								

Table 330: Ref ID: 2113 [Orth et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Orth SR, Schroeder T, Ritz E et al. Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. Nephrol Dial Transplant. 2005; 20(11):2414-2419. Ref ID: 2113	Prospective cohort Evidence level: 2 +	N total = 185 N smokers = 44 N never smokers = 141 1 centre study: Germany	**Inclusion:** patients with type 1 or 2 diabetes attending the clinic **Exclusion criteria:** people with GFR < 60 ml/min/1.73m^2, ex-smokers **Population baseline characteristics:** 60% had type 1 diabetes. 72% non-smokers and 86% smokers had proteinuria > 0.15 g/d. Smokers were significantly younger (47 vs.54 years), more likely to be male, and had a lower GFR than non-smokers (95 vs.107 ml/min). NS difference between smokers and non-smokers with respect to BMI, diabetes type 1, insulin use, duration of diabetes, HbA1c, retinopathy, proteinuria, hypertension, SBP, DBP, ACE inhibitors use, CAD, PVD, stroke.	Smokers N = 44 **Procedure:** At baseline, patients had a physical exam (BP, anthropometry, spot urine test, serum creatinine, cholesterol, triglycerides), an interview, and completed a standardised questionnaire to assess smoking status. GFR was estimated with MDRD equation. Patients had at least 4 annual follow-up visits. Patient management was left to GP in interim.	Never smokers N = 141 **Procedure:** As for intervention	Median 5.1 years	20% decline in GFR Change in proteinuria	Not stated

Effect size:

BP at baseline was well controlled for both smokers (135/80 mm Hg) and non-smokers (138/79 mm Hg) and improved during follow-up.

Effect of Smoking on GFR:GFR remained stable during follow-up in non-smokers (107 to 106 ml/min) but decreased significantly in smokers (95 to 83 ml/min, p<0.001). Smokers had a significantly increased odds of a 20% decline in GFR compared to non-smokers [OR 2.52 (95% CI 1.06 to 5.99), p<0.01]. This relationship persisted after

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
adjustment for diabetes type or control, retinopathy, age, BMI, ACE inhibitors use, BP, proteinuria (F-ratio=65.9, p<0.0001). Male gender and diabetes type independently influenced course of renal function in smokers compared to non-smokers. Male smokers had a significantly increased odds of a 20% decline in GFR compared with male non-smokers [OR 5.32 (95% CI 1.49 to 18.9), p<0.05]. Smokers with type 1 diabetes had a significantly increased odds of a 20% decline in GFR compared with non-smokers with type 1 diabetes [OR 4.49 (95% CI 1.36 to 14.7), p<0.05]. NS for presence or absence of retinopathy, proteinuria, or ACE inhibitors use. **Effect of Smoking on Proteinuria**: Proteinuria increased from baseline to the end of the study in smokers (0.36 to 0.44 g/24-h, N=44) and non-smokers (0.47 to 0.54 g/24-h, N=141), but there was NS differences between the two groups.								

Table 331: Ref ID: 4014 [Pechter 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pechter U, Ots M, Mesikepp S et al. Beneficial effects of water-based exercise in patients with chronic kidney disease. International Journal of Rehabilitation Research. 2003; 26(2):153-156. Ref ID: 4014	Non-randomised controlled trial Evidence level: 2 -	N total = 26 N water-based exercise = 17 N sedentary control = 9 1 centre study: Estonia	**Inclusion:** patients with moderate CKD **Exclusion criteria:** not stated **Population baseline characteristics:** NS differences between two groups for age, sex, BP, GFR (62 vs.69 ml/min, exercise vs.control), cystatin C, peak VO_2	N water-based exercise = 17 **Procedure:** At baseline and after 12 weeks of intervention, patients had a physical exam (BP, anthropometry, spot urine test, serum creatinine, cystatin C, triglycerides) and underwent a breath-by-breath bicycle cardiopulmonary test. Water-based aerobic exercise was performed twice/week for 30 minutes/session in a swimming pool. The control group maintained their mostly sedentary lifestyle. GFR was estimated with Cockcroft Gault equation.	N sedentary control = 9 **Procedure:** As for intervention	3 months	Change in GFR Change in cystatin C Change in proteinuria Cardiorespiratory parameters Blood lipids	Not stated
Effect size: **Change in GFR:** There were NS changes in GFR from baseline to 12 weeks in people who took aerobic water-based exercise (62.9 ml/min at baseline to 67.1 ml/min at 12 weeks, NS), and there were NS changes in GFR in the sedentary control group (69.8 ml/min at baseline to 66.3 ml/min at 12 weeks, NS).								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Change in cystatin C: Cystatin C significantly decreased in the exercise group (1.7 mg/l at baseline to 1.4 mg/l at 12 weeks, p<0.05), whereas there were NS changes in cystatin C in the sedentary control (1.7 mg/l at baseline to 2.0 mg/l at 12 weeks, NS) **Change in proteinuria :** Proteinuria significantly decreased in the exercise group (0.7 g/g PCR at baseline to 0.4 at 12 weeks, p<0.05), whereas there were NS changes in proteinuria in the sedentary control (1.4 mg/l g/g PCR at baseline to 1.5 at 12 weeks, NS) **Cardiorespiratory parameters:** Peak O2 pulse, peak ventilation, and peak load all significantly increased (improved) from baseline to 12 weeks in people who took aerobic water-based exercise (p<0.05), where as there were NS changes in these parameters in the sedentary control group. There were NS changes ion either group for peak VO2. **Blood lipids:** There were NS changes in either group for total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides **Note:** very small trial, no assessment of power, uneven distribution to each arm, not randomised, no mention of blinding, no mention of loss to follow-up								

Table 332: Ref ID: 527 [Perneger et al. 1999]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Perneger TV, Whelton PK, Puddey IB et al. Risk of end-stage renal disease associated with alcohol consumption. American Journal of Epidemiology. 1999; 150(12):1275-1281. Ref ID: 527	Case-control Evidence level: 2 - USA	N cases (people with new ESRD) =716 N controls (age matched from general population) = 361	**Inclusion:** Cases: people with new-onset ESRD requiring dialysis diagnosed between Jan.-July 1991 identified through ESRD registry. Controls: general population identified by random number dialling. **Exclusion criteria:** not stated **Population baseline characteristics:** NS difference between case (ESRD) and age matched controls (general population) with respect to age (47 years). 42% of cases were female, 65% controls were female. 54% of cases were black, only 14% of controls were black.	N=716 cases Increasing drinks/month or day **Procedure:** Age matching between cases and controls. Participants interviewed via telephone about alcohol consumption, amount, frequency, and potential confounders (diabetes, hypertension, acetaminophen use, cigarette smoking, drug use, income, education	N=361 controls Abstainer **Procedure:** As for intervention	N/A 90% of controls and 95% of cases completed the telephone interview	ESRD	Not stated
Effect size **Effect of Alcohol consumption on progression to ESRD:** Univariate analysis: Compared with abstainers (N=246 cases and N=124 controls), people who drank > 2 alcoholic drinks/day and ≤ 4 drinks/day (N=41 cases, N=7 controls) had a significantly greater odds of ESRD [OR 3.0 (95% CI 1.3 to 6.8)]								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Compared with abstainers (N=246 cases and N=124 controls), people who drank > 4 drinks/day (N=61 cases, N=5 controls) had a significantly greater odds of ESRD [OR 6.1 (95% CI 2.4 to 15.7)] After excluding N=68 people who drank moonshine and adjusting for age, sex, race, hypertension, income, diabetes, acetaminophen use, smoking, and opiate use (total N=912), people who drank > 2 alcoholic drinks/day had a significantly greater odds of ESRD [OR 4.0 (95% CI 1.2 to 13.0)] than abstainers. There was NS odds of ESRD for people who drank moderate amounts of alcohol (< 1 drink/day or 1-2 drinks/day) compared with abstainers (adjusted as above) **Note:** limitations – The following weren't addressed in the methodology: The same exclusion criteria are used for both cases and controls, Comparison is made between participants and non-participants to establish their similarities or differences. Cases are clearly defined and differentiated from controls. Is it clearly established that controls are non-cases? Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment.								

Table 333: Ref ID: 149 [Saiki 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Saiki A, Nagayama D, Ohhira M et al. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. International Journal of Obesity. 2005; 29(9):1115-1120. Ref ID: 149	Before and after prospective observational study Evidence level : 3 Japan	N =22	**Inclusion criteria:** obese (BMI > 25 kg/m^2) diabetic people with proteinuria (urinary albumin > 300 mg/day), serum creatinine < 265.2 micromol/l and diabetic retinopathy. **Exclusion criteria:** Unstable diabetic retinopathy, pleural effusion, severe leg edema **Baseline characteristics:** Mean age 53.6 years, BMI 30.4 kg/m^2, CrCl 0.68 ml/s/1.73 m^2	After low calorie formula diet N=22 **Procedure:** Patients all received a daily caloric intake of 25-30 kcal/kg and 0.8 g/kg protein for at least 3 months. Statins, antihypertensive agents permitted providing they were prescribed for more than 2 months prior to study and that the doses were unchanged. All patients then switched to a low calorie diet (740 or 970 kcal/day or 11-19 kcal/kg) for 4 weeks. A formula diet providing 170 kcal/pack was used. Patients either consumed one meal of formula diet and 2 ordinary meals (total 970 kcal/day) or 2 formula diet meals and 1 ordinary meal (total 740 kcal/day). Salt intake was 2.79 g/day (740 kcal diet) or 4.90 g/day (970 kcal diet) Plasma creatinine, CrCl (24-h urine collections) physical exam, weight, BP, BMI, and clinical chemistry tests performed at baseline and every week for 4 weeks. Visceral fat measured before and after 4 weeks.	Before low calorie formula diet N=22	1 month	Weight BMI Change in protein excretion Change in CrCl	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size **Body weight:** Weight significantly decreased after four weeks of a low calorie formula diet (85.2 kg at baseline to 79.0 kg after 4 weeks, p<0.0001) **BMI:** BMI significantly decreased after four weeks of a low calorie formula diet (30.4 kg/m^2 at baseline to 28.2 kg/m^2 after 4 weeks, p<0.0001) **BP:** SBP and DBP each significantly decreased (p<0.05) after four weeks of a low calorie formula diet. **Change in CrCl:** There was NS change in CrCl after four weeks of a low calorie formula diet (0.68 ml/s/1.73 m^2 at baseline to 0.77 after 4 weeks, p NS) **Change in serum creatinine:** Serum creatinine significantly decreased after 4 weeks of a low calorie-formula diet (172.4 micromol/l at baseline to 130.8 micromol/l after 4 weeks, p<0.0001) **Change in protein excretion:** Urinary protein significantly decreased after 4 weeks of a low calorie-formula diet (3.27 g/24-h at baseline to 1.50 g/24-h after 4 weeks, p<0.0001) Weight loss was significantly correlated with a decrease in serum creatinine (r=0.621, p=0.0021) and with a decrease in protein excretion (r=0.487, p=0.0215) Decrease in visceral fat was significantly correlated with decreases in serum creatinine (r=0.579, p=0.0475) and with a decrease in protein excretion (r=0.575, p=0.0496) Changes in BP (SBP or DBP) were NS correlated with changes in creatinine or urinary protein excretion. Assessment of bias: small study N=22 and all patients were hospitalised. Before and after study.								

Table 334: Ref ID: 1319 [Solerte et al. 1989]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Solerte SB. Effects of diet-therapy on urinary protein excretion albuminuria and renal haemodynamic function in obese diabetic patients with overt nephropathy. International Journal of Obesity. 1989;(2):203-211. Ref ID: 1319	Before and after prospective observational study Evidence level: 3 Italy	N =24	**Inclusion criteria:** obese type 1 and type 2 diabetic people with overt nephropathy (urinary protein excretion > 500 mg/day on six consecutive visits), and diabetic retinopathy. **Exclusion criteria:** Unstable diabetic retinopathy, pleural effusion, severe leg edema **Baseline characteristics:** NS different between type 1 and 2 diabetics, therefore results were pooled.	After low calorie diet N=24 **Procedure:** Prior to the study, all patients received a mean daily caloric intake of 1870 kcal/day (220 kg carbohydrate, 81 g protein, 63 g fat). All patients then switched to a low calorie diet (1410 kcal/day consisting of 170 g carbohydrate, 58 g protein, 49 g fat) for 12 months. Drugs for arterial hypertension were discontinued. Plasma creatinine, creatinine clearance, urinary protein excretion rate, urinary albumin excretion rate, GFR ($^{99}Tc^{m}$) physical exam, weight, BP, BMI, and clinical chemistry tests performed at baseline and after 12 months.	Before low calorie diet N=24	12 months	BMI Change in protein excretion Change in albumin excretion Change in CrCl Change in GFR	Not stated
Effect size:								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

BMI: BMI significantly decreased after 12 months of a low calorie diet (33.5 kg/m^2 at baseline to 26.2 kg/m^2 after 12 months, p<0.001)

BP: SBP and DBP each significantly decreased (p<0.002) after 12 months of a low calorie diet.

Blood lipids: Total cholesterol (p<0.01) and triglycerides (p<0.002)significantly decreased and HDL cholesterol (p< 0.05) significantly increased after 12 months of a low calorie diet.

Change in CrCl: CrCl significantly increased after 12 months of low calorie diet (80 ml/min/1.73 m^2 at baseline to 90 ml/min/1.73 m^2 after 12 months, p<0.01)

Change in GFR: GFR significantly increased after 12 months of low calorie diet (64 ml/min/1.73 m^2 at baseline to 80 ml/min/1.73 m^2 after 12 months, p<0.01).

Change in serum creatinine: Serum creatinine significantly decreased after 12 months of a low calorie diet (145.2 micromol/l at baseline to 101.2 micromol/l after 12 months, p<0.001)

Change in protein excretion: Urinary protein excretion significantly decreased by 51% after 12 months of a low calorie diet, p<0.01. Reduction was seen in all 24 patients. 5/24 had UPE below overt nephropathy levels after 12 months of low calorie diet.

Change in albumin excretion: Urinary albumin excretion significantly decreased by 31% after 12 months of a low calorie diet, p<0.01.

Weight loss was NS correlated with a decrease in UPE or UAE.

Changes in BP (SBP or DBP) were NS correlated with decreases in urinary protein excretion or UAE..

Assessment of bias: small study N=24. Before and after study.

Q.5.11 Optimal blood pressure ranges (2014 guideline – chapter 10.1)

Table 335: Ref ID: 211 [Jafar et al. 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jafar TH, Stark PC, Schmid CH et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis.[see comment]. Annals of Internal Medicine.	Meta-analysis Search MEDLINE from 1977 to 1999 Evidence level 1 +	11 RCT (N=1860)	**Inclusions**: AIPRD Study Group database: RCTs of at least 1 year follow-up in patients with nondiabetic kidney disease, in which ACE inhibitors are compared to other antihypertensive regimens. **Exclusion:** acute kidney failure, immunosuppressive drug use, congestive heart failure, obstructive uropathy, renal artery stenosis, active systemic disease, diabetes, transplantation, allergy to ACE inhibitors, pregnancy	Follow-up SBP < 110 mm Hg (N*=253) Follow-up SBP 120-129 mm Hg (N*=959) Follow-up SBP 130-139 mm Hg (N*=1220) Follow-up SBP 140-159 mm Hg (N*=1501) Follow-up SBP >160 mm Hg (N*=1088) *Number of patients with even a single SBP in the corresponding range **Procedure:**Patients randomised to ACE inhibitors or other antihypertensive treatments to	Follow-up SBP 110-119 mm Hg (N*=548)	2.2 years.	Primary Outcome: doubling of serum creatinine or initiation of dialysis	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
2003; 139(4):244-252.				achieve goal BP of < 140/90 mm Hg. Justification for pooling placebo-controlled trials and active-drug controlled trials is based on the presence of pre-existing hypertension and the use of antihypertensive agents in most patients in the control groups to achieve a BP goal < 140/90 mm Hg				

Effect size:

Primary Outcome: Kidney Disease Progression (doubling of serum creatinine or initiation of dialysis)

Multivariate analysis: baseline and achieved SBP were significantly associated with kidney disease progression (p<0.001 for both). Baseline DBP (p=0.006) and achieved DBP (p=0.007) also significantly associated with kidney disease progression. Baseline and achieved urinary protein excretion also significantly associated with kidney disease progression (p<0.001, for both).

A. Reference SBP 110-119 mm Hg

- People with nondiabetic kidney disease with SBP < 110 mm Hg (N=253) had a significantly increased risk of kidney disease progression compared to people in the reference range 110-119 mm Hg (N=548) [RR 2.48 (95% CI 1.07 to 5.77)]
- People with nondiabetic kidney disease with SBP 120-129 mm Hg (N=959) had NS risk of kidney disease progression compared to people in the reference range 110-119 mm Hg (N=548).
- People with nondiabetic kidney disease with SBP 130-139 mm Hg (N=1220) had NS risk of kidney disease progression compared to people in the reference range 110-119 mm Hg (N=548) [RR 1.83 (95% CI 0.97 to 3.44)].
- People with nondiabetic kidney disease with SBP 140-159 mm Hg (N=1501) had an increased risk of kidney disease progression compared to people in the reference range 110-119 mm Hg (N=548) [RR 2.08 (95% CI 1.13 to 3.86)].
- People with nondiabetic kidney disease with SBP ≥ 160 mm Hg (N=1088) had an increased risk of kidney disease progression compared to people in the reference

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

range 110-119 mm Hg (N=548) [RR 3.14 (95% CI 1.64 to 5.99)].

Authors state that the lowest risk of kidney progression was at SBP 110-129 mm Hg. SBP of 130 mm Hg or more were associated with a steep increase in risk. Note that risk is NS at 130-139 mm Hg.

B. Reference urine protein excretion < 0.5 d/day

- People with nondiabetic kidney disease and urine protein excretion of 0.5 to 1.9 g/day (N=1863) had NS risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022).
- People with nondiabetic kidney disease and urine protein excretion of 2.0 to 2.9 g/day (N=629) had a significantly increased risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022) [RR 1.67 (95% CI (1.09 -2.54)].
- People with nondiabetic kidney disease and urine protein excretion of 3.0 to 3.9 g/day (N=423) had a significantly increased risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022) [RR 2.25 (95% CI (1.43 -3.53)].
- People with nondiabetic kidney disease and urine protein excretion of 4.0 to 4.9 g/day (N=320) had a significantly increased risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022) [RR 3.43 (95% CI (2.09 -5.64)].
- People with nondiabetic kidney disease and urine protein excretion of 5.0 to 5.9 g/day (N=194) had a significantly increased risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022) [RR 3.41 (95% CI (1.91 -6.06)].
- People with nondiabetic kidney disease and urine protein excretion of ≥ 6.0 g/day (N=234) had a significantly increased risk of kidney disease progression compared to people in the reference range urine protein excretion < 0.5 d/day (N=1022) [RR 4.77 (95% CI (2.92 -7.81)].

C. Protein excretion and SBP (reference 110 -119 mm Hg)

- For people with urine protein excretion < 1g/day, there was NS risk for renal disease progression at any level of blood pressure (The risk increased, but NS, at > 160 mm Hg or < 110 mm Hg).
- For people with urine protein excretion ≥ 1 g/day, there was NS risk for renal disease progression when SBP was 120-129 mm Hg [RR 2.0, NS].
- For people with urine protein excretion ≥ 1 g/day, there was a significantly increased risk for renal disease progression when SBP was 130-139 mm Hg [RR 4.5, no CI given)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

- For people with urine protein excretion ≥ 1 g/day, there was a significantly increased risk for renal disease progression when SBP was 140-159 mm Hg [RR 5.5, no CI given)
- For people with urine protein excretion ≥ 1 g/day, there was a significantly increased risk for renal disease progression when SBP was > 160 mm Hg [RR 8.5, no CI given).

D. Assignment to ACE inhibitors significantly decreases kidney disease progression [RR 0.67 (95% CI 0.53 to 0.84)].

Authors conclusion: recommend a SBP target of 110-129 in people with urine protein excretion of > 1g/day. SBP < 110 mm Hg is associated with increased risk of kidney disease progression.

Table 336: Ref ID: 3667 [Klahr et al. 1994]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Klahr S, Levey AS, Beck GJ et al. The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease. The New England Journal of Medicine. 1994; 330(13):877-884.	RCT Evidence level: 1 + 15 US nephrology practices All analyses were ITT.	Total N =840 Study 1 N= 585 Study 2 N= 255	**Inclusions:** Study 1: age 18 to 70 years, serum creatinine 1.2 to 7.0 mg/dl (women) or 1.4 to 7.0 mg/dl (men) or a creatinine clearance < 70 dietary ml/min/1.73 m^2 , MAP < 125 mm Hg (normotensive people were included) **Study 1:** GFR 25 to 55 ml/min/1.73 m^2, dietary protein intake ≥ 0.9 g/kg, MAP < 125 mm Hg **Study 2:** GFR 13 to 24 ml/min/1.73 m^2, MAP < 125 mm Hg **Exclusion:** pregnancy, body weight under 80% or over 160% standard body weight, diabetes requiring insulin, urinary protein excretion > 10 g/d, history	Low mean arterial pressure (MAP ≤ 92 mm Hg for people 18-60 y or ≤ 98 mm Hg for people 61 and older) equivalent to 125/75 mm Hg Study 1 (GFR 25 to 55 ml/min/1.73 m^2) N= 300 Study 2 (GFR 13 to 24 ml/min/1.73 m^2) N= 132 **Protocol:** In study 1 and 2, patients were randomised to usual BP or to a lower mean arterial pressure goal. In study 1, patients were also randomised to a usual protein diet (1.3 g protein and 16-20 mg phosphorus/kg per day) or a low protein diet (0.58 g protein and 5-10 mg phosphorus/kg each day). In Study 2, in addition to BP randomisation, patients were also randomised to a low protein diet or	Usual mean arterial pressure (≤ 107 mm Hg for people 18-60 y or ≤ 113 mm Hg for people o 61 and older) equivalent to 140/90 mm Hg Study 1 N= 285 Study 2 N= 123 **Protocol:** as for intervention	2.2 years (mean) 1.9% dropout Study 1 1.2% dropout Study 2	Rate of change of GFR (slope) Composite outcome: ESRD or death	National Institute of Diabetes and Digestive and Kidney Diseases, Health Care Financing Administration

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			of renal transplant or chronic conditions. **Baseline population characteristics:** In either Study 1 or Study 2, there was NS difference at baseline between people assigned to usual MAP or low MAP for GFR, creatinine clearance, serum creatinine, SBP, DBP, age (52 yr) **Study 1:** baseline GFR was 38.6 ml/min/1.73 m^2 **Study 2**: baseline GFR was 18.5 ml/min/1.73 m^2	a very low protein diet (0.28 g protein and 4-9 mg phosphorus/kg each day supplemented by a keto acid-amino acid mix of 0.28 g/kg per day) The BP targets were reached using ACE inhibitor with or without a diuretic, and CCB and other medications were added as needed. Protein intake was assessed monthly by 24-h urinary excretion of urea nitrogen and by dietary records. BP, creatinine clearance, urinary protein excretion measured at baseline and every month thereafter. GFR was assessed by renal clearance of ^{125}I-iothalamate at baseline, at 2 months, at 4 months, and every 4 months thereafter.				
Effect size: There were NS interactions between the BP and dietary interventions. Thus, BP effects were pooled in the low and usual protein diet (Study 1) or the low and very low protein diet (Study 2).								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

At follow-up in Study 1 and Study 2, the mean blood pressure difference between the low and usual MAP groups was 4.7 mm Hg (p<0.001)

Low (≤ 92 mm Hg) vs.Usual (≤ 107 mm Hg) MAP

Decline in GFR

In study 1 (N=585, GFR 25 to 55 ml/min/1.73 m^2) the mean GFR decline was significantly faster in the low MAP group than the usual MAP group in the first 4 months following randomisation (3.4 ml/min per 4 months compared to 1.9 ml/min per 4 months, p =0.01).

However, there was no significant difference in GFR decline between low and usual MAP from baseline to 3 years of follow-up. The mean decline was 1.6 ml/min less in the low pressure group (p=0.18)

Similarly, in Study 2 (N=255, GFR 13 to 24 ml/min/1.73 m^2), there was NS difference in GFR decline between people randomised to low versus usual MAP. The mean decline was 0.5 ml/min per year less in the low pressure group (p=0.28)

STUDY 1 (GFR 25 to 55 ml/min/1.73 m^2): There was an effect of baseline urinary protein excretion and BP control on GFR decline.

In subgroup analysis of people with baseline urinary protein < 1g/day (N=420), was there NS difference in GFR decline between low and usual MAP after 3 years.

In subgroup analysis of people with baseline urinary protein excretion 1 to <3 g/day (N=104), there was a moderate benefit of low MAP (GFR decline 4.5 ml/min/year) on declining GFR compared with usual MAP (GFR decline 6 ml/min/year) (no p value given).

In subgroup analysis of people with baseline urinary protein excretion > 3 g/day (N=54), there was a large benefit of low MAP (GFR decline 7 ml/min/year) on declining GFR compared with usual MAP (GFR decline 10.5 ml/min/year) (no p value given).

STUDY 2 (GFR 13 to 24 ml/min/1.73 m^2): There was an effect of baseline urinary protein excretion and BP control on GFR decline.

In subgroup analysis of people with baseline urinary protein < 1g/day (N=136), was there NS difference in GFR decline between low and usual MAP after 3 years.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
In subgroup analysis of people with baseline urinary protein excretion 1 to <3 g/day (N=63), there was NS difference in GFR decline between low and usual MAP after 3 years In subgroup analysis of people with baseline urinary protein excretion > 3 g/day (N=32), there was a benefit of low MAP (GFR decline 5.5 ml/min/year) on declining GFR compared with usual MAP (GFR decline 8 ml/min/year) (no p value given). In subgroup analysis of black and white people, black patients (N=53) had a significantly greater GFR decline (19 ml/min over 3 years) compared with white people (N=525, 11 ml/min over 3 years) (p=0.02). There was NS difference between low and usual MAP for projected GFR decline in the black patient population. In subgroup analysis of types of renal disease, people with polycystic kidney disease had a faster decline in GFR than people with other renal diseases (17 versus 10 ml/min over 3 years, p<0.001). There was no benefit to assignment to low MAP in people with PKD. **Composite outcome: ESRD or death** Study 2: There was NS difference between low or usual MAP for the risk of death or ESRD. There was NS difference between low or usual MAP for the number of deaths or stopping points (rapidly declining GFR, progression to ESRD) in either study. **Note:** GFR decline was slow and the study would need a longer follow-up to detect differences between treatment arms. Patients with high baseline proteinuria (> 1g/d) benefit from low BP								

Table 337: Ref ID: 86 [Ruggenenti et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ruggenenti P, Perna A, Loriga G et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet. 2005; 365(9463):939-946.	RCT Open label Evidence level: 1 + Multicentre study Italy All analyses were ITT.	N = 338	**Inclusions:** REIN-2 trial (Ramipril Efficacy in Nephrology) - people age 18 to 70 years with non-diabetic nephropathy and persistent proteinuria (urinary protein excretion > 1 g/24-h for at least 3 months) who had not received ACE for at least 6 weeks prior to inclusion. Patients with proteinuria 1 to 3 g/24-h were included if their creatinine clearance < 45 ml/min/1.73 m^2. Patients with proteinuria ≥ 3 g/24-h were included if their creatinine clearance < 70 ml/min/1.73 m^2. **Exclusion:** use of NSAIDs/immunosuppressive drugs/corticosteroids, acute MI or cerebrovascular accident in previous 6 months, severe uncontrolled hypertension, renovascular disease, obstructive uropathy, diabetes, collagen disease, cancer, chronic cough,	Intensive BP control (SBP < 130 mm Hg, DBP < 80 mm Hg) N= 167 **Protocol:** 6 week washout from ACE, ARB, and dihydropyridine calcium channel blockers. Baseline BP, creatinine clearance, 24-h urinary protein excretion measured. 6 week ramipril run-in (2.5 -5.0 mg/d). Repeated baseline measurements. Randomisation to conventional BP control (DBP < 90 mm Hg, irrespective of SBP) or intensive BP control (SBP < 130 mm Hg, DBP < 80 mm Hg). Intensive BP control to be achieved with addition of felodipine (5-10 mg/d). Other antihypertensive	Conventional BP control (DBP < 90 mm Hg, irrespective of SBP) N=168 **Protocol:** as for intervention	3 years (median follow-up 19 months)	Primary outcome: ESRD Rate of decline of GFR Proteinuria All-cause mortality Non-fatal serious adverse events	Mario Negri Institute for Pharmacological Research.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			drug/alcohol abuse, pregnancy, poor tolerance/allergy to ACE inhibitors or dihydropyridine calcium channel blockers **Baseline population characteristics:** NS differences at baseline between those randomised to intensive or conventional BP control for age, gender, GFR, creatinine clearance, urinary protein excretion, SBP, DBP, MAP, serum K+	drugs (not ACE, ARB, or CCB) added if BP target was not reached. BP measured at 1, 2 weeks, and 3 months post-randomisation, and every 3 months thereafter. GFR was assessed by renal clearance of iohexol at baseline and at 3 and 6 months.				

Effect size:

Intense vs.Conventional BP

During follow-up, mean SBP was 129.6 ± 10.9 mm Hg and mean DBP was 79.5 ± 5.3 mm Hg in the intensive BP group. Mean SBP was 133.7 ± 12.6 mm Hg and mean DBP was 82.3 ± 7.1 mm Hg in the conventional BP group. A mean separation of 3.0 mm Hg in SBP was maintained throughout the study.

Primary Outcome: ESRD

There was NS difference in the risk of ESRD between intensive (23% progressed to ESRD) vs.conventional (20% progressed to ESRD) BP control.

In subgroup analysis of people with baseline proteinuria ≥ 3 g/24-h, there was NS difference in the risk of ESRD for intensive (N=58) versus conventional (N=62) BP control.

In subgroup analysis of people with baseline proteinuria 1 to 3 g/24-h, there was NS difference in the risk of ESRD for intensive (N=109) versus conventional (N=106) BP

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Change in GFR There was NS difference in median GFR decline between those with intensive (N=93) BP control compared to those with conventional (N=80) BP control. **Urinary protein excretion** There was NS difference in urinary protein excretion between those with intensive (N=167) BP control compared to those with conventional (N=168) BP control. **All-cause mortality** 2 deaths (1 MI, 1 unknown cause) in intensive BP control compared to 3 deaths (1 MI, 1 stroke, 1 cancer) in conventional BP control group. This study may be underpowered for statistical analysis for this outcome. **Non-fatal serious adverse events** 37 nonfatal SAE arose in the intense BP control group compared with 25 nonfatal SAE in the conventional BP group. This study may be underpowered for statistical analysis for this outcome.								

Table 338: Ref ID: 216 [Bakris et al. 2003]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bakris GL, Weir MR, Shanifar S et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study.[see comment]. Archives of Internal Medicine. 2003; 163(13):1555-1565	Post-hoc of double blind RCT Evidence level: 2+ Reduction of Endponts in NIDDM with the Angiotensin II Antatgonist Losartan-RENAAL) Multinational trial	N=1513	**Inclusion:** RENAAL Study: Type 2 diabetes with nephropathy (presence on 2 occasions of urinary albumin:creatinine ratio of at least 300 mg/g (800 mg/day), serum creatinine between 1.3 and 3.0 mg/dl, with a lower limit of 1.5 mg/dl for male participants weighing more than 60 kg **Exclusion:** none stated **Baseline population characteristics:** There was NS difference between BP in the losartan or placebo group. Baseline BP was 152/82 mm Hg in the losartan group and 153/82 mm Hg in the placebo group. 75% of the participants had Stage 3 or 4 CKD.	SBP 130-139 mm Hg (N=209) SBP 140-159 mm Hg (N=610) SBP 160-179 mm Hg (N=373) SBP ≥ 180 mm Hg (N=152) **Protocol:** Patients were stratified by baseline proteinuria (< 2000 mg/g or ≥ 2000 mg/g) and then randomised to receive losartan potassium (N=751; 50 mg/d) or placebo (N=762; usual care). BP target was < 140/90 mm Hg. To achieve target BP study drugs were up-titrated, followed by additional open-label antihypertensive therapy. SBP and DBP were determined at baseline and throughout study	SBP < 130 mm Hg (N=169) **Protocol:** as for intervention	Median follow-up 3.4 yrs	Primary endpoint: time to doubling of serum creatinine, ESRD, or death ESRD or death ESRD alone	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

Hazard ratios are set as the lowest category of SBP.

Primary endpoint: time to doubling of serum creatinine, ESRD, or death

BASELINE DBP:

- There was NS increase in risk for the primary endpoint at any level of baseline DBP.

LAST DBP Prior to Endpoint (Achieved DBP):

- There was NS increase in risk for the primary endpoint at achieved DBP 70-89 mm Hg.
- Achieved DBP of 90-99 mm Hg (N=152) were associated with a significantly higher risk of reaching the combined renal endpoint compared to achieved DBP < 70 mm Hg (N=365). [HR 1.72 (95% CI 1.32 to 2.23), p<0.001]
- Achieved DBP of ≥ 100 mm Hg (N=38) were associated with a significantly higher risk of reaching the combined renal endpoint compared to achieved DBP < 70 mm Hg (N=365) [HR 2.54 (95% CI 1.70 to 3.80), p<0.001]

BASELINE SBP:

- The risk of doubling serum creatinine, ESRD, or death increases with increasing baseline SBP.
- There was NS difference for the combined renal endpoint between people with baseline SBP 130-139 mm Hg (N=209) compared to people with baseline SBP < 130 mm Hg (N=169).
- There was NS difference for the combined renal endpoint between people with baseline SBP 140-159 mm Hg (N=610) compared to people with baseline SBP < 130 mm Hg (N=169). [HR 1.28 (95% CI 0.97 to 1.69), p=0.08]
- People with baseline SBP 160-179 mm Hg (N=373) had a significantly higher risk of reaching the combined renal endpoint compared to people with baseline SBP < 130 mm Hg (N=169) [HR 1.82 (95% CI 1.36 to 2.42), p<0.001]
- People with baseline SBP ≥ 180 mm Hg (N=152) had a significantly higher risk of reaching the combined renal endpoint compared to people with baseline SBP < 130 mm Hg (N=169) [HR 1.85 (95% CI 1.33 to 2.57), p<0.001].

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Kaplan-Meier curve for baseline SBP < 140 mm Hg versus baseline SBP ≥ 140 mm Hg.

- People with baseline SBP ≥ 140 mm Hg had a significantly higher risk of reaching the combined renal endpoint than people with SBP < 140 mm Hg [HR 1.66, p<0.001]

LAST SBP Prior to Endpoint (Achieved SBP)

- There was NS difference for the combined renal endpoint between people with achieved SBP 130-139 mm Hg (N=401) compared to people with achieved SBP < 130 mm Hg (N=278).
- People with achieved SBP 140-159 mm Hg (N=522) had a significantly higher risk of reaching the combined renal endpoint compared to people with achieved SBP < 130 mm Hg (N=278) [HR 1.49 (95% CI 1.18 to 1.90), p=0.001]
- People with achieved SBP 160-179 mm Hg (N=158) had a significantly higher risk of reaching the combined renal endpoint compared to people with achieved SBP < 130 mm Hg (N=278) [HR 2.74 (95% CI 2.12 to 3.54), p<0.001]
- People with achieved SBP ≥ 180 mm Hg (N=71) had a significantly higher risk of reaching the combined renal endpoint compared to people with achieved SBP < 130 mm Hg (N=278) [HR 3.51 (95% CI 2.50 to 4.93), p<0.001]

PULSE PRESSURE- the difference between SBP and DBP

- A baseline pulse pressure ≥ 70 mm Hg significantly increased the risk of reaching the combined renal endpoint compared to people with baseline PP < 60 mm Hg.

ESRD or death

BASELINE DBP:

- There was NS increase in risk for ESRD or death at any level of baseline DBP.
- Every 10 mm Hg rise in baseline DBP decreased the risk for ESRD or death by 10.9 % (p=0.01) (multivariate model adjusted for urinary ACR (log scale), creatinine, albumin, hemoglobin).

LAST DBP Prior to Endpoint (Achieved DBP):

- There was NS increase in risk for ESRD or death at achieved DBP 70-89 mm Hg.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

- Achieved DBP of 90-99 mm Hg (N=144) were associated with a significantly higher risk of reaching ESRD or death compared to achieved DBP < 70 mm Hg (N=377). [HR 1.55 (95% CI 1.16 to 2.08), p=0.003]
- Achieved DBP of ≥ 100 mm Hg (N=36) were associated with a significantly higher risk of reaching ESRD or death compared to achieved DBP < 70 mm Hg (N=377) [HR 2.74 (95% CI 1.78 to 4.24), p<0.001]

BASELINE SBP:

- There was NS difference for reaching ESRD or death between people with baseline SBP 130-139 mm Hg (N=209) compared to people with baseline SBP < 130 mm Hg (N=169).
- There was NS difference for reaching ESRD or death between people with baseline SBP 140-159 mm Hg (N=209) compared to people with baseline SBP < 130 mm Hg (N=169). [HR 1.38 (95% CI 0.99 to 1.91), p=0.06]
- People with baseline SBP 160-179 mm Hg (N=373) had a significantly higher risk of reaching ESRD or death compared to people with baseline SBP < 130 mm Hg (N=169) [HR 1.96 (95% CI 1.40 to 2.74), p<0.001]
- People with baseline SBP ≥ 180 mm Hg (N=152) had a significantly higher risk of reaching ESRD or death compared to people with baseline SBP < 130 mm Hg (N=169) [HR 2.10 (95% CI 1.44 to 3.06), p<0.001].
- Every 10 mm Hg rise in baseline SBP increased the risk for ESRD or death by 6.7% (p=0.007) (multivariate model adjusted for urinary ACR (log scale), creatinine, albumin, hemoglobin).

LAST SBP Prior to Endpoint (Achieved SBP):

- The risk of reaching ESRD or death increased significantly for people with an achieved SBP > 140 mm Hg.
- There was NS difference in risk for reaching ESRD or death between people with achieved SBP 130-139 mm Hg (N=392) compared to people with achieved SBP < 130 mm Hg (N=286).
- People with achieved SBP 140-159 mm Hg (N=518) had a significantly higher risk of reaching ESRD or death compared to people with achieved SBP < 130 mm Hg (N=286) [HR 1.33 (95% CI 1.02 to 1.72), p=0.03]

PULSE PRESSURE:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

- A baseline pulse pressure ≥ 70 mm Hg significantly increased the risk of reaching ESRD or death compared to people with baseline PP < 60 mm Hg.

ESRD alone

BASELINE DBP:

- There was NS increase in risk for ESRD alone at any level of baseline DBP.

LAST DBP Prior to Endpoint (Achieved DBP)

- There was NS increase in risk for ESRD alone at achieved DBP 70-89 mm Hg.
- Achieved DBP of 90-99 mm Hg (N=144) were associated with a significantly higher risk of reaching ESRD compared to achieved DBP < 70 mm Hg (N=377). [HR 1.67 (95% CI 1.15 to 2.44), p=0.008]
- Achieved DBP of ≥ 100 mm Hg (N=36) were associated with a significantly higher risk of reaching ESRD compared to achieved DBP < 70 mm Hg (N=377) [HR 3.26 (95% CI 1.90 to 5.58), p<0.001]

BASELINE SBP:

- There was NS difference for reaching ESRD alone between people with baseline SBP 130-139 mm Hg (N=209) compared to people with baseline SBP < 130 mm Hg (N=169).
- There was NS difference for reaching ESRD alone between people with baseline SBP 140-159 mm Hg (N=209) compared to people with baseline SBP < 130 mm Hg (N=169). [HR 1.37 (95% CI 0.90 to 2.10), p=0.14]
- People with baseline SBP 160-179 mm Hg (N=373) had a significantly higher risk of reaching ESRD alone compared to people with baseline SBP < 130 mm Hg (N=169) [HR 2.13 (95% CI 1.39 to 3.27), p<0.001]
- People with baseline SBP ≥ 180 mm Hg (N=152) had a significantly higher risk of reaching ESRD alone compared to people with baseline SBP < 130 mm Hg (N=169) [HR 2.02 (95% CI 1.24 to 3.29), p=0.005].
- Kaplan-Meier curve for baseline SBP < 140 mm Hg versus baseline SBP ≥ 140 mm Hg.
- People with baseline SBP ≥ 140 mm Hg had a significantly higher risk of reaching ESRD alone than people with SBP < 140 mm Hg [HR 1.72, p<0.001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
LAST SBP Prior to Endpoint (Achieved SBP) • The risk of reaching ESRD increased significantly for people with an achieved SBP > 140 mm Hg. • There was NS difference in risk for reaching ESRD alone between people with achieved SBP 130-139 mm Hg (N=392) compared to people with achieved SBP < 130 mm Hg (N=286). • People with achieved SBP 140-159 mm Hg (N=518) had a significantly higher risk of reaching ESRD alone compared to people with achieved SBP < 130 mm Hg (N=286) [HR 1.52 (95% CI 1.07 to 2.15), p=0.02] PULSE PRESSURE: • A baseline pulse pressure ≥ 70 mm Hg significantly increased the risk of reaching ESRD alone compared to people with baseline PP < 60 mm Hg **Note:** Authors suggest a target SBP < 140 mm Hg. Note that bias is possible because the analysis is retrospective and BP was not measured using a random zero device. Also, analysis of achieved BP (measured before an endpoint) may be subject to interpretation bias. Comparator group (< 130 mm Hg SBP) had fewer participants than other SBP groups.								

Table 339: Ref ID: 70 [Berl et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Berl T, Hunsicker LG, Lewis JB et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. Journal of the American Society of Nephrology. 2005; 16(7):2170-2179.	Post-hoc of RCT Evidence level: 2+ (Irbesartan in Diabetic Nephropathy IDNT data)	N=1590	**Inclusion:** 30-70 yrs, Type 2 diabetes, hypertension defined as any of; seated office SBP > 135 mmHg, seated office DBP > 85 mm Hg or documented treatment with antihypertensive agents. All patients had diabetic nephropathy with overt proteinuria (> 900 mg/24 hr) and mild-to-moderate renal insufficiency (serum creatinine between 88 and 266 µmol/l (1.0 and 3.0 mg/dl) in women and 106 and 266 µmol/l (1.2 and 3.0 mg/dl) in men. **Exclusion:** none stated **Baseline population characteristics:** Baseline BP was 159/87 mm Hg and it decreased with NS differences between them, in the amlodipine, irbesartan, and placebo groups. 30% reached the 135 mm Hg SBP goal, and 81% achieved the 85 mm Hg DBP goal.	Achieved SBP ≤ 120 mm Hg (N=53) Protocol: Patients randomised to receive irbesartan (300 mg/d), amlodipine (10 mg/day) or placebo (usual care). BP target was < 135/85 mm Hg in all 3 arms. To achieve target BP participants were prescribed additional antihypertensive therapy. SBP and DBP were determined at baseline and throughout study	Achieved SBP > 120 mm Hg (N= 1537) Protocol: as for intervention	Median follow-up 2.9 yrs Follow-up until ESRD, death, censoring in Dec., 2000.	All-cause mortality Cardiovascular mortality Congestive heart failure Myocardial infarction Stroke	Bristol-Meyers Squibb and Sanofi-Synthelabo
Effect size: **All-cause mortality** People with an achieved SBP ≤ 120 mm Hg (N=53) had a significantly greater risk of all-cause mortality compared to people with an achieved SBP > 120 mm Hg								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

(N=1537) [RR 3.05 (95% CI 1.80 to 5.17), p<0.0001]

There was NS association between DBP and risk for all-cause mortality.

Cardiovascular mortality

There was a decrease in risk for cardiovascular mortality as achieved SBP decreased from > 170 mm Hg to 120 to 130 mm Hg. A 20 mm Hg lower achieved SBP was associated with a 39% reduction in cardiovascular mortality (p<0.002).

There was a significant decrease in risk for cardiovascular mortality in people with SBP 120-130 mm Hg compared to the reference range 130-140 mm Hg (no numerical data provided, no p value).

There was a significantly higher risk for cardiovascular mortality in people with SBP > 170 mm Hg compared to the reference range 130-140 mm Hg (no numerical data provided, no p value).

People with an achieved SBP ≤ 120 mm Hg (N=53) had a significantly greater risk of cardiovascular mortality compared to people with an achieved SBP > 120 mm Hg (N=1537) [RR 4.06 (95% CI 2.11 to 7.80), p<0.0001].

There was NS association between DBP and risk for cardiovascular mortality.

Congestive heart failure

There was a decrease in risk for congestive heart failure as achieved SBP decreased from > 170 mm Hg to 120 to 130 mm Hg. A 20 mm Hg lower achieved SBP was associated with a 25% reduction in the risk for congestive heart failure (p=0.001).

People with an achieved SBP 120 to 130 mm Hg had a significantly reduced risk of congestive heart failure compared to the reference range SBP 130-140 mm Hg (no numerical data provided, no p value).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

People with an achieved SBP ≤ 120 mm Hg (N=53) had a significantly greater risk of congestive heart failure compared to people with an achieved SBP > 120 mm Hg (N=1537) [RR 1.80 (95% CI 1.17 to 2.86), p=0.008]

There was NS association between DBP and risk for congestive heart failure.

Myocardial infarction

People with an achieved SBP ≤ 120 mm Hg (N=53) had NS risk of MI compared to people with an achieved SBP > 120 mm Hg (N=1537).

SBP was NS related to the risk of nonfatal MI.

A 10 mm Hg lower achieved DBP was associated with a significantly higher risk of MI [RR 1.61 (95% CI 1.28 to 2.02), p<0.0001]

Compared to the reference DBP 70-80 mm Hg, the risk for MI was significantly higher in people with DBP < 70 mm Hg (no numerical data provided, no p value).

Compared the reference DBP 70-80 mm Hg, the risk for MI was significantly lower in people with DBP > 85 mm Hg (no numerical data provided, no p value).

Stroke

People with an achieved SBP ≤ 120 mm Hg (N=53) had NS risk of stroke compared to people with an achieved SBP > 120 mm Hg (N=1537).

SBP was NS related to the risk of stroke.

A 10 mm Hg lower achieved DBP was associated with a significantly lower risk of stroke [RR 0.65 (95% CI 0.48 to 0.88), p=0.005]

Note: People with SBP ≤ 120 mm Hg were more likely to have a history of heart disease and CHF at baseline and were younger, took fewer CCB, had lower serum creatinine, lower baseline SBP and DBP, and took fewer antihypertensive agents than people with SBP > 120 mm Hg. However, the risks of death and CV death were significant and were not decreased after accounting for the different frequencies of these co-morbidities.

Table 340: Ref ID: 504 [Peterson et al. 1995]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Annals of Internal Medicine. 1995; 123(10):754-762.	Posthoc analysis RCT Evidence level: 2 + 15 US nephrology practices All analyses were ITT.	Total N =840 Study 1 N= 585 Study 2 N= 255	**Inclusions:** Study 1: age 18 to 70 years, serum creatinine 1.2 to 7.0 mg/dl (women) or 1.4 to 7.0 mg/dl (men) or a creatinine clearance < 70 dietary ml/min/1.73 m^2 , MAP < 125 mm Hg (normotensive people were included) **Study 1:** GFR 25 to 55 ml/min/1.73 m^2, dietary protein intake ≥ 0.9 g/kg, MAP < 125 mm Hg **Study 2:** GFR 13 to 24 ml/min/1.73 m^2, MAP < 125 mm Hg **Exclusion:** pregnancy, body weight under 80% or over 160% standard body weight, diabetes requiring insulin, urinary protein	Low mean arterial pressure (MAP ≤ 92 mm Hg for people 18-60 y or ≤ 98 mm Hg for people 61 and older) equivalent to 125/75 mm Hg Study 1 (GFR 25 to 55 ml/min/1.73 m^2) N= 300 Study 2 (GFR 13 to 24 ml/min/1.73 m^2) N= 132 **Protocol:** In study 1 and 2, patients were randomised to usual BP or to a lower mean arterial pressure goal. In study 1, patients were also randomised to a usual protein diet (1.3 g protein and 16-20 mg phosphorus/kg per day) or a low protein diet (0.58 g protein and 5-10 mg phosphorus/kg each day). In Study 2, in addition to BP randomisation, patients were also randomised to a low protein diet or a	Usual mean arterial pressure (≤ 107 mm Hg for people 18-60 y or ≤ 113 mm Hg for people o 61 and older) equivalent to 140/90 mm Hg Study 1 N= 285 Study 2 N= 123 **Protocol:** as for intervention	2.2 years (mean)	Rate of change of GFR (slope) Change in proteinuria	National Institute of Diabetes and Digestive and Kidney Diseases, Healh Care Financing Administration

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			excretion > 10 g/d, history of renal transplant or chronic conditions. **Baseline population characteristics:** In either Study 1 or Study 2,there was NS difference at baseline between people assigned to usual MAP or low MAP for GFR, creatinine clearance, serum creatinine, SBP, DBP, age (52 yr) **Study 1:** baseline GFR was 38.6 ml/min/1.73 m^2 **Study 2:** baseline GFR was 18.5 ml/min/1.73 m^2	very low protein diet (0.28 g protein and 4-9 mg phosphorus/kg each day supplemented by a keto acid-amino acid mix of 0.28 g/kg per day) The BP targets were reached using ACE inhibitor with or without a diuretic, and CCB and other medications were added as needed. Protein intake was assessed monthly by 24-h urinary excretion of urea nitrogen and by dietary records. BP, creatinine clearance, urinary protein excretion measured at baseline and every month thereafter. GFR was assessed by renal clearance of ^{125}I-iothalamate at baseline, at 2 months, at 4 months, and every 4 months thereafter.				
Effect size: There were NS interactions between the BP and dietary interventions. Thus, BP effects were pooled in the low and usual protein diet (Study 1) or the low and very low protein diet (Study 2). **Low (≤ 92 mm Hg) vs.Usual (≤ 107 mm Hg) MAP**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Decline in GFR according to baseline proteinuria

In study 1 (GFR 25 to 55 ml/min/1.73 m^2), there was NS difference in GFR decline between low and usual MAP in people with baseline proteinuria < 0.25 g/d (mean 0.08 g/d, N=301). There was NS difference in GFR decline between low and usual MAP in people with baseline proteinuria 0.25 -1.0 g/d (mean 0.58 g/d, N=119). For people with baseline proteinuria of 1.0-3.0 g/day (mean 1.8 g/d, N=104), the GFR decline was slower in those randomised to low MAP control than those assigned to usual MAP control after 2 years follow-up (no p value given). For people with baseline proteinuria of > 3.0 g/day (mean 4.8 g/d, N=54), the GFR decline was significantly slower in those randomised to low MAP control than those assigned to usual MAP control (no p value given).

Study 1: In patients with baseline proteinuria of 0.25 to 3.0 g/day, the association of higher blood pressure with faster GFR decline was apparent at 98 mm Hg MAP. Inpatients with baseline proteinuria > 3.0 g/day, the association of higher blood pressure with faster GFR decline was apparent at 92 mm Hg MAP.

In study 2 (GFR 13 to 24 ml/min/1.73 m^2) there was NS difference between low and usual MAP for GFR decline in people with baseline proteinuria < 1.0 g/d (N=136). People with baseline proteinuria > 1.0 g/d (N=95) had faster GFR decline and benefited from low MAP versus usual MAP (no p value given). This was particularly seen in people with baseline proteinuria > 3.0 g/d (N=32)

Change in Proteinuria

Assignment to low MAP significantly decreased proteinuria during follow-up compared to usual MAP. This was seen in people with baseline proteinuria > 0.25 g/day

Authors conclusion: that people with proteinuria > 3 g/day benefit from BP control at 92 mm Hg MAP and people with proteinuria 0.25 to 3 g/day benefit from BP control at 98 mm Hg MAP or less.

Table 341: Ref ID: 75 [Pohl et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. Journal of the American Society of Nephrology. 2005; 16(10):3027-3037.	Post-hoc of RCT Evidence level: 2+ (Irbesartan in Diabetic Nephropathy IDNT data)	N=1590	**Inclusion:** 30-70 yrs, Type 2 diabetes, hypertension defined as any of; seated office SBP > 135 mm Hg, seated office DBP > 85 mm Hg or documented treatment with antihypertensive agents. All patients had diabetic nephropathy with overt proteinuria (> 900 mg/24 hr) and mild-to-moderate renal insufficiency (serum creatinine between 88 and 266 µmol/l (1.0 and 3.0 mg/dl) in women and 106 and 266 µmol/l (1.2 and 3.0 mg/dl) in men. **Exclusion:** none stated **Baseline population characteristics:**Baseline BP was 159/87 mm Hg and it decreased with NS differences between the amlodipine, irbesartan, and placebo groups. 30% reached the 135 mm Hg SBP goal, and 81% achieved the 85 mm Hg DBP goal.	Achieved SBP **Protocol:** Patients randomised to receive irbesartan (300 mg/d), amlodipine (10 mg/day) or placebo (usual care). BP target was < 135/85 mm Hg in all 3 arms. To achieve target BP participants were prescribed additional antihypertensive therapy. SBP and DBP were determined at baseline and throughout study	Baseline SBP **Protocol:** as for intervention	Median follow-up 2.9 yrs Follow-up until ESRD, death, censoring in Dec., 2000.	Composite Outcome: Doubling of baseline serum creatinine or ESRD All-cause mortality	Bristol-Meyers Squibb and Sanofi-Synthelabo
Effect size: **BP**								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

BP was controlled to similar means in the 3 groups (irbesartan group 141/78±14/8; amlodipine group 142/77±13/8; placebo/usual care group 144/80±13/8 mmHg).

Renal Endpoint: Doubling of baseline serum creatinine or ESRD

*Baseline BP

Baseline SBP correlated significantly with the renal outcomes (doubling of SCr or ESRD) in univariate analysis. The risk for reaching a renal endpoint increased progressively with higher baseline SBP ($p<0.0001$).

36% of those in the highest quartile (baseline SBP > 170 mm Hg) reached a renal endpoint vs. 18% of those in the lowest quartile (SBP < 145 mm Hg).

Baseline DBP was NS correlated with renal outcome, with no correlation for those with baseline DBP > 100 mmHg.

*Achieved SBP

Achieved follow-up SBP is an independent predictor of the risk for a adverse renal outcomes irrespective of the baseline BP. A decrease of 20 mm Hg in achieved SBP was associated with a 47% decrease in the risk for developing a renal end point.

While baseline SBP was an independent predictor of renal outcome, this relationship was lost when achieved SBP was taken into account.

Mean follow-up seated SBP grouped in 10 mm Hg increments were considered with the natural log of the relative risk of reaching a renal end point. This showed an increasing risk with increasing SBP, though outcomes for those with a follow-up SBP <120 were not substantially better than those with a follow-up between 120 and 130 mm Hg.

Baseline estimated GFR and albumin/creatinine ratio (ACR) were both linearly and significantly correlated with both mean follow-up BP and with the risk of renal endpoint.

The assessed risk for a renal outcome 20 mm Hg decrease in SBP was associated with a 47% decrease in the risk of renal outcome ($p<0.0001$). After correlation for eGFR and ACR each 20 mm Hg decrease in SBP was still associated with a 30% reduction in the risk for a renal event ($p<0.0001$), independent of these two baseline renal covariates.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
All-cause mortality								
The natural log of the relative risk for all cause mortality shows an essentially linear relationship from SBP of 120 to SBP > 180 mm Hg, however participants with the lowest SBP < 120 mm Hg had a sharply higher mortality.								

Table 342: Ref ID: 314 [Hovind et al. 2001]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hovind P, Rossing P, Tarnow L et al. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. [see comment]. Kidney International. 2001; 60(1):277-283.	Case series Evidence level: 3 One centre, Steno Diabetes Center Denmark All analyses were ITT.	N = 301	Inclusions: Type 1 diabetic patients with nephropathy (persistent albuminuria > 200 microgram/min in at least two out of three consecutive 24-h urine collections, presence of diabetic retinopathy, absence of other kidney or renal tract disease) Exclusion: not stated Baseline population characteristics: NS differences at baseline between remission group and non-remission group for age, diabetes duration, SBP, DBP, GFR. Baseline MAP was lower in remission group (102 vs.104 mm Hg, p<0.05). There were more males in the non-remission group. NS differences at baseline between regression and non-	Remission Group (N=92) Regression Group (N=67) Protocol: 301 Type 1 diabetics with nephropathy were observed for 7 years. GFR was measured annually by plasma clearance of ^{51}Cr-EDTA. Albuminuria (24-h urine collections), BP, blood glucose, weight, insulin and antihypertensive agent dosage was monitored at baseline and every 4 months. The BP target was < 140/90 mm Hg, mostly achieved with ACE inhibitors (179/271).	Non-remission group (N=209) Non-regression Group (N=234)	7 years	Principal endpoint: Regression (a rate of decline in GFR ≤ 1 ml/min/year during the observation period – equivalent to natural decline with aging) Surrogate endpoint: Remission (decrease in albuminuria < 200 microgram/min in at least two out of three consecutive 24-h urine collections that was sustained for at least one year during follow-up,	Danish Diabetes Association, Hansen Foundation, Henriksen Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			regression groups for sex, age, diabetes duration, GFR. Baseline SBP, DBP, and MAP were lower in the regression group than the non-regression group.				with a decrease of at least 30% from pre-remission levels).	

Effect size:

Of the 271 people treated with antihypertensive drugs, 43% achieved a mean SBP < 140 mm Hg and 83% achieved a DBP < 90 mm Hg. 40% achieved < 140/80 mm Hg.

The mean decline in GFR in all 301 patients during follow-up was 4.0 ± 0.2 ml/min/year.

Surrogate endpoint: Remission (decrease in albuminuria < 200 microgram/min in at least two out of three consecutive 24-h urine collections that was sustained for at least one year during follow-up, with a decrease of at least 30% from pre-remission levels).

- 31% of the cohort (92/301) obtained remission.
- During follow-up, the GFR decline was significantly less in the remission group (N=92, GFR decline 2.2 ml/min/year) than in the non-remission group (N=209, GFR decline 4.8 ml/min/year, p<0.001)
- Follow-up SBP was significantly less in the remission group (N=92, SBP 137 mm Hg) than in the non-remission group (N=209, SBP 145 mm Hg, p<0.001)
- Follow-up DBP was significantly less in the remission group (N=92, DBP 81 mm Hg) than in the non-remission group (N=209, DBP 84 mm Hg, p<0.001)
- Follow-up MAP was significantly less in the remission group (N=92, MAP 100 mm Hg) than in the non-remission group (N=209, MAP 105 mm Hg, p<0.001)
- More people with a lower follow-up MAP achieved remission. Stratified by MAP: MAP 93 mm Hg (58% remission), MAP 99 mm Hg (33% remission), MAP 103 mm Hg (25% remission), MAP 107 mm Hg (20% remission), MAP 113 mm Hg (17% remission)

Principal endpoint: Regression (a rate of decline in GFR ≤ 1 ml/min/year during the observation period – equivalent to natural decline with aging)

- 22% (67/301) of the cohort obtained regression.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• Follow-up SBP was significantly less in the regression group (N=67, SBP 138 mm Hg) than in the non-regression group (N=234, SBP 144 mm Hg, p<0.001) • Follow-up DBP was significantly less in the regression group (N=67, DBP 80 mm Hg) than in the non-regression group (N=234, DBP 84 mm Hg, p<0.001) • Follow-up MAP was significantly less in the regression group (N=67, MAP 99 mm Hg) than in the non-regression group (N=234, MAP 104 mm Hg, p<0.001) • More people with a lower follow-up MAP achieved regression. Stratified by MAP: MAP 93 mm Hg (42% regression), MAP 99 mm Hg (32% regression), MAP 103 mm Hg (11% regression), MAP 107 mm Hg (20% regression), MAP 113 mm Hg (17% regression) • The adjusted odds ratio for regression associated with a 10 mm Hg decline in MAP was 2.14 (95% CI 1.33 to 3.44, p<0.001). • The adjusted odds ratio for regression associated with a tenfold lowering of albuminuria was 2.79 (95% CI 1.35 to 5.69, p<0.001). • The adjusted odds ratio for regression associated with a reduction of 1% in haemoglobin HbA1c was 2.00 (95% CI 1.46 to 2.73, p<0.001). **Note:** authors suggest aggressive antihypertensive treatment induces remission and regression in Type 1 diabetics with nephropathy. Lower MAP, reduced albuminuria, and good glycaemic control were predictors of regression of nephropathy.								

Table 343: Ref ID: 41 [Kovesdy et al. 2006]

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Kovesdy CP, Trivedi BK, Kalantar ZK et al. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. Nephrology Dialysis Transplantation. 2006; 21(5):1257-1262.</td><td>Case series

Evidence level: 3

US War veterans cohort</td><td>N = 860</td><td>Inclusions: CKD cohort: US veterans enrolled at the Nephrology Clinic at Salem Veterans Affairs Medical Centre between 1990 and 2004 with Stage 3-5 CKD (< 60 ml/min/1.73 m^2), not yet on dialysis.

Exclusion: Stage 1-2 CKD

Baseline population characteristics:
<table>
<tr><th>Characteristic</th><th>CKD cohort</th></tr>
<tr><td>N</td><td>860</td></tr>
<tr><td>Age, year</td><td>68</td></tr>
<tr><td>% black race</td><td>24.4</td></tr>
<tr><td>% male</td><td>99.1</td></tr>
<tr><td>% diabetes</td><td>50</td></tr>
<tr><td>eGFR, ml/min/1.73 m^2</td><td>32</td></tr>
<tr><td>Serum albumin, g/dl</td><td>3.5</td></tr>
</table>
People with SBP < 133 mm Hg were less likely to be black or to be on antihypertensive drugs and more likely to have atherosclerotic cardiovascular</td><td>SBP 133-154 mm Hg
N= 238

SBP 155-170 mm Hg
N= 211

SBP > 170 mm Hg
N= 194

Protocol: BP, antihypertensive medication use, serum creatinine, albumin, haemoglobin, 24-h urine protein or PCR were measured at first clinic visit. Deaths were recorded from the US Dept. of Veteran Affairs CPRS.</td><td>SBP < 133 mm Hg,

N=217

Protocol: as for intervention</td><td>Patients were followed until they died, were lost to follow-up, or until May 15, 2005.</td><td>Primary outcome: all-cause mortality</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			disease (ASCVD) and CHF, and more likely to have have lower proteinuria					

Effect size:

Older age, ASCVD, ejection fraction < 35%, smoking, lower eGFR, lower serum albumin, lower proteinuria, diabetes, and being on dialysis were all associated with higher mortality.

Aim: Determine relationship between SBP and all-cause mortality in a CKD (GFR < 60 ml/min/1.73 m^2) male cohort.

Reference: SBP < 133 mm Hg

Primary Outcome: All-cause mortality

- Mortality was highest in men with CKD and SBP < 133 mm Hg. Mortality was lowest in men with CKD and SBP 134-154.
- Men with SBP 134-154 mm Hg (N=238) had a significantly decreased risk for all-cause mortality compared with men who had SBP < 133 mm Hg (N=217) [adjusted HR 0.62 (95% CI 0.45 to 0.85), p=0.003] (fully adjusted model for age, race, diabetes history, CHF, ASCVD, use of antihypertensive agents, eGFR, BMI, smoking, serum albumin, cholesterol, hemoglobin, 24-h urinary protein).
- Men with SBP 155-170 mm Hg (N=211) had a significantly decreased risk for all-cause mortality compared with men who had SBP < 133 mm Hg (N=217) [adjusted HR 0.63 (95% CI 0.45 to 0.87), p=0.006]
- Men with SBP > 170 mm Hg (N=194) had a significantly decreased risk for all-cause mortality compared with men who had SBP < 133 mm Hg (N=217) [adjusted HR 0.69 (95% CI 0.49 to 0.96), p=0.029]

Primary Outcome: All-cause mortality: Determine relationship between DBP and all-cause mortality in a CKD (GFR < 60 ml/min/1.73 m^2) male cohort.

- Mortality was highest in men with DBP < 64 mm Hg and lowest in men with DBP > 86 mm Hg.
- Compared to men with DBP < 65 mm Hg (N=233), there was NS difference in risk for all-cause mortality for men with DBP 65-75 mm Hg (N=197).
- Compared to men with DBP < 65 mm Hg (N=233), there was NS difference in risk for all-cause mortality for men with DBP 76-86 mm Hg (N=230).
- Compared to men with DBP < 65 mm Hg (N=233), there was a significant reduction in the risk for all-cause mortality for men with DBP > 86 mm Hg (N=200) [adjusted HR 0.6 (95% CI 0.4 to 0.9, p=0.005).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• A 10 mm Hg higher DBP was associated with a hazard ratio for all-cause mortality of 0.87 (95% CI 0.80-0.94, p=0.002)								

Table 344: Ref ID: 6 [Van et al. 2006]

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>van BT, Woittiez K, Blauw GJ et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. J Am Soc Nephrol. 2006; 17(9):2561-2566.</td><td>Case series

Evidence level: 3

Netherlands population based elderly cohort study</td><td>N = 550</td><td>Inclusions: inhabitants of Leiden age 85 followed up until age 90 or death. No selection criteria for health or demographic characteristics.

Exclusion: none stated

Baseline population characteristics:
<table><tr><th>Characteristic</th><th>Leiden cohort</th></tr><tr><td>N</td><td>550</td></tr><tr><td>Age, year</td><td>85</td></tr><tr><td>Mean creatinine clearance, ml/min</td><td>45.4</td></tr><tr><td>% female</td><td>66</td></tr><tr><td>% diabetes</td><td>16</td></tr><tr><td>% hypertension</td><td>40</td></tr><tr><td>% chronic disease</td><td>41</td></tr><tr><td>% with no cardiovascular disease</td><td>37</td></tr><tr><td>% with 1 cardiovascular disease</td><td>38</td></tr><tr><td>% with 2 cardiovascular diseases</td><td>19</td></tr></table></td><td>DBP 70-79 mm Hg
N=219

DBP 80-89 mm Hg
N=148

DBP ≥ 90 mm Hg
N=48

Protocol: At baseline and yearly thereafter, BP, weight, creatinine clearance (Jaffe method and Cockcroft-Gault equation) was measured. ECG, interviews, and performance tests also done. Medical history obtained from participant’s physician</td><td>DBP < 70 mm Hg,

N= 135
Baseline SBP 120-129 mm Hg

N=276

Protocol: as for intervention</td><td>5 years</td><td>Change in creatinine clearance</td><td>Dutch Ministry of Health, Welfare and Sports</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			SBP, mm Hg	155.6					
			DBP, mm Hg	76.9					
			Pulse pressure, mm Hg	8.7					

Effect size:

- During follow-up to age 90 or death, the overall decline in creatinine clearance was 1.31 ml/min per year, p<0.001
- At baseline and follow-up, creatinine clearance was correlated with the presence of cardiovascular disease. Creatinine clearance declined an extra 0.21 ml/min per year, p=0.002 over the normal annual decline for every additional manifestation of cardiovascular disease.
- There was no association between either SBP or pulse pressure and the annual decline in creatinine clearance.
- DBP < 70 mm Hg versus DBP 70-79 mm Hg or DBP 80-89 or DBP ≥ 90 mm Hg in an elderly cohort (85-90 y).

Creatinine Clearance

- The decline in creatinine clearance was significantly faster in people with DBP < 70 mm Hg (-1.63 ml/min, N= 135) compared to people with DBP 70-79 mm Hg (-1.21 ml/min, N=219, p=0.01)
- The decline in creatinine clearance was significantly faster in people with DBP < 70 mm Hg (-1.63 ml/min, N= 135) compared to people with DBP 80-89 mm Hg (-1.26 ml/min, N=219, p=0.03)
- There was NS difference in declining creatinine clearance between people with DBP < 70 mm Hg compared to people with DBP ≥ 90 mm Hg (N=48)

NOTE: DBP < 70 mm Hg is associated with a decline in creatinine clearance, whereas higher DBP is not. Authors acknowledge that CG is not the gold standard for assessing renal function; also that they did not have data on heart failure rates

Table 345: Ref ID: 2846 [Weiner et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Weiner DE, Tighiouart H, Levey AS et al. Lowest systolic blood pressure is associated with stroke in stages 3 to 4 chronic kidney disease. Journal of the American Society of Nephrology. 2007; 18(3):960-966.	Case series Evidence level: 3 small group, no power assessment US cohort (pooled Atherosclerosis Risk in Community Study (ARIC) and Cardiovascular Health	N = 1549 CKD defined GFR < 60 ml/min/1.73 m^2.	**Inclusions:** ARIC enrolled people age 45 to 64 from four US communities between 1987 and 1989. CHS enrolled people age 65 and older from four US communities between 1989 and 1990. Analysis restricted to people with CKD (GFR < 60 ml/min/1.73 m^2.) People with diabetic or nondiabetic CKD, hypertensive or normotensive. **Exclusion:** Stage 5 CKD (GFR < 15 ml/min/1.73 m^2). **Baseline population characteristics:** **Characteristic** / **CKD cohort** N / 1549 Age, year / 70.2 % black race / 13.8 % female / 57.0 % CHS cohort / 73.4 % diabetes / 17.9 % hypertension / 73.5	Baseline SBP < 120 mm Hg, N= 416 **Protocol:** GFR measured using MDRD after calibrating ARIC and CHS laboratories indirectly using NHANES III data.	Baseline SBP 120-129 mm Hg N=276 **Protocol:** as for intervention	8.8 years	Primary outcome: definite or probable incident stroke (defined as sudden/rapid onset of neurologic symptoms lasting > 24 h or led to death in absence of evidence of non-stroke cause)	NIH NIDDK grants, Amgen

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Study (CHS)		% coronary disease	14.6					
			SBP, mm Hg	135.2					
			DBP, mm Hg	71.5					
			Serum creatinine, mg/dl	1.3					
			eGFR, ml/min/1.73 m^2	51.2					
			Serum albumin, g/dl	3.9					
			% All-cause stroke	12.3					

Effect size:

Determine relationship between baseline SBP and incident stroke in a CKD (GFR < 60 ml/min/1.73 m^2) cohort.

Baseline SBP < 120 mm Hg versus Baseline SBP 120-129 mm Hg in a CKD (GFR < 60 ml/min/1.73 m^2) cohort.

Primary Outcome: Stroke

People with CKD and SBP < 120 mm Hg were at a significantly increased risk for stroke compared with people with CKD and SBP 120-129 mm Hg [HR 2.26 (95% CI 1.16 to 4.41)] (fully adjusted model for age, race, gender, diabetes history, coronary disease history, LVH, use of antihypertensive agents, education, smoking, serum albumin, non-HDL cholesterol, haemoglobin, study origin).

This is a J-shaped curve for risk of stroke with increasing BP.

In sensitivity analysis (multivariate), people with CKD and SBP < 120 mm Hg who used antihypertensive agents (N=209) had a significantly increased risk of stroke compared with people with CKD and SBP 120-129 mm Hg who used antihypertensive agents (N=173) [HR 2.62 (95% CI 1.22 to 5.66)]

There was NS difference for the risk of stroke between people with CKD and SBP < 120 mm Hg who did not use antihypertensive agents (N=207) compared with people with CKD and SBP 120-129 mm Hg who did not use antihypertensive agents (N=103). However, this study lacked statistical power due to its small size (N).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
NOTE: Authors acknowledge that there is NO data on proteinuria and analysis is mostly applicable to Stage 3 CKD in a US population. Authors caution against concluding that antihypertensive agent use in people with CKD and SBP < 120 mm Hg CAUSES the increased stroke risk as it is likely that these people may have a greater lifetime CVD burden and therefore higher stroke risk.								

Table 346: Ref ID: 117 [Sarnak et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sarnak MJ, Greene T, Wang X et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study.[see comment]. Annals of Internal Medicine. 2005; 142(5):342-	Long-term follow-up of MDRD trial (cohort study) Evidence level: 2 - 15 US nephrology practices All analyses were ITT.	Total N =840 Study 1 N= 585 Study 2 N= 255	**Inclusions:** Study 1: age 18 to 70 years, serum creatinine 1.2 to 7.0 mg/dl (women) or 1.4 to 7.0 mg/dl (men) or a creatinine clearance < 70 dietary ml/min/1.73 m^2 , MAP < 125 mm Hg (normotensive people were included) **Study 1:** GFR 25 to 55 ml/min/1.73 m^2, dietary protein intake ≥ 0.9 g/kg, MAP < 125 mm Hg **Study 2:** GFR 13 to 24 ml/min/1.73 m^2, MAP < 125 mm Hg **Exclusion:** pregnancy, body weight under 80% or over 160% standard body weight, diabetes requiring insulin, urinary protein excretion > 10 g/d, history of renal transplant or	Low mean arterial pressure (MAP ≤ 92 mm Hg for people 18-60 y or ≤ 98 mm Hg for people 61 and older) equivalent to 125/75 mm Hg Combined Study 1 and Study 2 N= 432 **Protocol:** Trial was conducted from 1989 to 1993. In study 1 and 2, patients were randomised to usual BP or to a lower mean arterial pressure goal. Long-term follow-up: NO specific BP target was recommended after completion of the trial in 1993. BP was only measured once (at 9 months after the end of the trial). NO more BP measurements	Usual mean arterial pressure (≤ 107 mm Hg for people 18-60 y or ≤ 113 mm Hg for people o 61 and older) equivalent to 140/90 mm Hg Combined Study 1 and Study 2 N= 408 **Protocol:** as for intervention	Long-term follow-up (1993-2000) (censoring on Dec. 31, 2000) Mean duration was 6.2 years	Kidney Failure (defined as initiation of dialysis or renal transplantation) Composite outcome: Kidney Failure or all-cause mortality	National Institute of Diabetes and Digestive and Kidney Diseases

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
351.			chronic conditions. **Baseline population characteristics:** In either Study 1 or Study 2, NS difference at baseline between people assigned to usual MAP or low MAP for GFR, creatinine clearance, serum creatinine, SBP, DBP, age (52 yr) **Study 1:** baseline GFR was 38.6 ml/min/1.73 m^2 **Study 2:** baseline GFR was 18.5 ml/min/1.73 m^2	available thereafter and no way of knowing if the BP differences were maintained in the two trial arms. Also, no specific pharmacological therapy was recommended after trial completion. There was no way of knowing how the two trial arms differed during the 6 year follow-up after the trial officially ended. Onset of kidney failure ascertained from US Renal Data System and mortality from the National Death Index.				

Effect size:

Low (≤ 92 mm Hg) vs.Usual (≤ 107 mm Hg) MAP

Progression to Kidney Failure (initiation of dialysis or renal transplantation)

People with CKD originally assigned to the low MAP group had a significantly lower risk of progression to kidney failure compared to people with CKD originally assigned to the usual MAP [adjusted HR 0.68 (95% CI 0.57 to 0.82), P<0.001).

People with lower baseline proteinuria (< 1g/day) had a significantly lower risk of progression to kidney failure compared to people with baseline proteinuria > 1 g/day [HR 0.79 (95% CI 0.63 to 0.99), p=0.04).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Composite outcome: Kidney Failure or all-cause mortality People with CKD originally assigned to the low MAP group had a significantly lower risk of progression to kidney failure or all-cause mortality compared with people with CKD originally assigned to the usual MAP [adjusted HR 0.77 (95% CI 0.65 to 0.91), P=0.0024). There was NS difference in risk for progression to kidney failure or all-cause mortality between people with baseline proteinuria (< 1g/day) compared to people with baseline proteinuria > 1 g/day.								

Q.5.12 Practicalities of treatment with ACE inhibitors /ARBs in people with CKD (2014 guideline – chapter 10.3)

Table 347: Ref ID: 3676 [Bakris et al. 2000]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern?	Systematic review Search not stated Evidence level: 1 +	N=12 RCTs, 6 large double-blind, placebo controlled RCTs, 6 smaller randomised studies N=1102 people randomised to ACE inhibitor. N=705/1102 (64%)	**Inclusion: s**tudies had to be randomised to either ACE inhibitor therapy or blood pressure control using ACE inhibitors as part of the drug regimen, blood pressure goals < 140/90 mm Hg, with the majority of participants having > 25% loss of renal function at baseline, regardless of cause. Studies had to have a minimum	ACE inhibitors	Not applicable	mean follow-up of 3.2 years	Change in serum creatinine levels or GFR Hyperkalaemia	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arch Intern Med. 2000; 160(5):685-693.		had renal function data at both < 6 months and at study end	follow-up of 2 years. **Exclusion:** not stated					

Effect size:

Purpose: to examine changes in serum creatinine and potassium upon commencement of ACE inhibitors and to determine if increases in serum creatinine result in long-term protection against decline in renal function in people with CKD.

Serum Creatinine Levels

Initiation of ACE inhibitor or ARB is associated with a 30% or less increase (above baseline) in serum creatinine levels. This increase will occur within the first 2 weeks of treatment and usually stabilises within 2 to 4 weeks. In N=11 studies, the GFR decline was slower at the end of the study than after ACE initiation.

In 2 long-term studies in diabetic CKD populations, (n= 65) initiation of ACE inhibitor treatment resulted in a 3 to 9% reduction in GFR (below baseline). After 6 years of therapy, the GFR returned to levels not significantly different from baseline within 1 month of stopping ACE inhibitor treatment. Thus the initial and persistent decline in GFR is reversible despite prolonged ACE use.

Despite the initial decline in GFR (or increase in serum creatinine), people with the greatest degree of renal insufficiency receive the greatest protection from renal disease progression from ACE therapy. In people with serum creatinine > 2.0 mg/dl (> 177 micromol/L) there was a 62% to 75% decrease in renal progression. However, there is limited data on the benefit of ACE inhibitors in advanced disease (GFR < 30 ml/min).

Compared to the general population, people > 65 years of age or < 49.5 kg have much lower GFRs for a particular serum creatinine concentration.

Hyperkalaemia

In people with diabetic or nondiabetic renal disease (serum creatinine levels 133-265 micromol/L or 1.5 -3.0 mg/dl), serum potassium levels increased by 0.4 to 0.6 mmol/L during ACE inhibitor or ARB treatment. Approximately 1 to 1.7% developed hyperkalaemia > 6 mmol/l. The risk is low for hyperkalaemia

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
The authors present an algorithm. • A. Upon ACE initiation if serum creatinine does not change, continue to titrate ACE until BP goal reached. Check creatinine and potassium within 3-4 weeks. If stable, recheck annually. If NSAID started or hypoperfusion state develops, re-check more often. • B. If serum creatinine increases > 30% above baseline and BP goal is achieved recheck creatinine in 2-3 weeks. If the level is still > 30% reduce ACE dosage by 50% and add other antihypertensive agents to reach BP goal. Re-check creatinine in 4 weeks. If stable, monitor annually. If > 30% rise discontinue ACE and use other antihypertensive agents to reach BP goal. • C. If serum creatinine > 50% increase exclude hypoperfusion state (volume depletion and NSAID use), renal scan/angiogram to rule out bilateral renal artery stenosis.								

Q.5.13 Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD (2014 guideline – chapter 13.1)

Table 348: Ref ID: 44 [Chonchol et la. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey.[see comment]. Kidney	Cross-sectional population study NHANES III US population study Evidence Level: 3	N total =14679 N GFR ≥ 90 ml/min/ 1.73m^2= 9687 N GFR 60-89 ml/min/ 1.73m^2= 4094 N GFR 30-59	**Inclusion criteria**: a general health survey was conducted in USA in 1988-1994 of non-institutionalised adults 20 years or older. Random selection using a stratified cluster method. **Exclusion criteria:** CKD stage 5, GFR or vitamin D unusually high	N/A **Procedure:** Non-Hispanic blacks, elderly, and American Mexicans were deliberately over-sampled. Participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the MDRD equation re-calibrated to the MDRD laboratory.	N/A	N/A	Serum 25-hydroxyvitamin D [25 (OH) D_3]	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
International. 2007; 71(2):134-139. Ref ID: 44		ml/min/ 1.73m^2= 854 N GFR 15-29 ml/min/ 1.73m^2= 44	**Baseline Characteristics:** 44% non-Hispanic white, 28% non-Hispanic black, 28% Mexican-American, 77% received no vitamin D supplementation, 17% received > 400 IU/day vitamin D	Serum 25 (OH) D_3 was measured by a radioimmunoassay after extraction with acetonitrile. CKD was defined according to GFR and staged according to KDOQI.				

Effect size:

adjusted for age, sex, ethnicity, BMI, physical activity, vitamin D supplementation, milk consumption

In this American sample (N=14679), the prevalence of mild CKD (GFR 60-89 ml/min/1.73m^2) was 28%. The prevalence of moderate CKD (GFR 30-59 ml/min/1.73m^2) was 6% and the prevalence of severe CKD (GFR 15-29 ml/min/1.73m^2) was 0.2%.

GFR and Serum Vitamin D:

- Compared with people with GFR ≥ 90 ml/min/1.73m^2 (N= 9687, mean 25 (OH) D_3 = 73.3 nmol/l), people with GFR 60-89 ml/min/1.73m^2 (N= 4094, mean 25 (OH) D_3 = 77.3 nmol/l, p=0.0002) had significantly higher 25 (OH) D_3.
- Compared with people with GFR ≥ 90 ml/min/1.73m^2 (N= 9687, mean 25 (OH) D_3 = 73.3 nmol/l), there was NS difference in serum 25 (OH) D_3 for people with GFR 30-59 ml/min/1.73m^2 (N= 854, mean 25 (OH) D_3 = 75.8 nmol/l, p=0.10).
- Compared with people with GFR ≥ 90 ml/min/1.73m^2 (N= 9687, mean 25 (OH) D_3 = 73.3 nmol/l), people with GFR 15-29 ml/min/1.73m^2 (N= 44, mean 25 (OH) D_3 = 61.6 nmol/l, p=0.0002, mean difference -11.7 nmol/l) had significantly lower 25 (OH) D_3.

Note: Limitations –Cross-sectional analysis.

Table 349: Ref ID: 1225 [Craver et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Craver L, Marco MP, Martinez I et al. Mineral metabolism parameters throughout chronic kidney disease stages 1-5 - Achievement of K/DOQI target ranges. Nephrol Dial Transplant. 2007; 22(4):1171-1176. Ref ID: 1225	Cross-sectional study Two nephrology clinics, Spain Evidence Level: 3	N total =1836 N CKD Stage 1 = 174 N CKD Stage 2 = 341 N CKD Stage 3 = 856 N CKD Stage 4 = 354 N CKD Stage 5 = 111	**Inclusion criteria:** all CKD patients attending 2 nephrology clinics in Spain (similar treatment policies in each clinic) **Exclusion criteria:** history of primary parathyroid disease, previous parathyroidectomy, neoplasias, osteoporosis under treatment with bisphosphonates or calcitonin. **Baseline Characteristics:** None of the patients were on dialysis or received 25-vitamin D supplements. Significant differences among CKD stages were seen for gender, age, serum creatinine, creatinine clearance, Ca, P, Ca x P product, iPTH, treatment with Ca salts and/or calcitriol, and 1, 25 OH_2 D_3 . NS differences for CKD aetiology, diabetes and 25 (OH) D_3.	N/A **Procedure:** Medication use, age, gender, CKD aetiology, presence of diabetes, serum creatinine, phosphate, calcium, Ca X P product, and iPTH were determined. Serum 1, 25 OH_2 D_3 (N=522) determined with radioreceptor assay (Hybritec, normal range 18-78 pg/ml). Serum 25 (OH) D_3 (N=205) determined in October-February with radioimmunoassay (Biosource, normal range 12-80 ng/ml). Serum iPTH determined by a two-site electrochemiluminometric assay (Cobast Roche, normal range 1.2-6.9 pmol/l). Creatinine clearance determined by Cockcroft Gault equation.	N/A	N/A)	Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH_2 D_3) Serum 25-hydroxyvitamin D [25 (OH) D_3]	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size:

Changes in serum iPTH and 1,25 Vit D precede changes in calcium or phosphate.

Serum Ca: Mean levels of Ca increased from CKD Stages 1 to 3 and decreased thereafter. People with Stage 4 CKD (N=354, mean Ca 9.35 mg/dl) had significantly lower serum calcium than people with Stage 3 CKD (N=856, mean Ca 9.57 mg/dl, p<0.05).

Serum P: Mean levels of P remained stable from Stages 1 to 3 CKD and then increased thereafter. People with Stage 4 CKD (N=354, mean P 3.92 mg/dl) had significantly higher serum phosphate than people with Stage 3 CKD (N=856, mean P 3.59 mg/dl, p<0.05). People with Stage 5 CKD (N=111, mean P 4.89 mg/dl) had significantly higher serum phosphate than people with Stage 4 CKD (N=354, mean P 3.92 mg/dl, p<0.05).

Serum iPTH: Serum iPTH increased steadily across all stages of CKD.

- People with Stage 2 CKD (N=341, mean iPTH 5.97 pmol/l) had significantly higher serum iPTH than people with Stage 1 CKD (N=174, mean iPTH 4.86 pmol/l, p<0.05).
- People with Stage 3 CKD (N=856, mean iPTH 8.96 pmol/l) had significantly higher serum iPTH than people with Stage 2 CKD (N=341, mean iPTH 5.97 pmol/l, p<0.05).
- People with Stage 4 CKD (N=354, mean iPTH 16.47 pmol/l) had significantly higher serum iPTH than people with Stage 3 CKD (N=856, mean iPTH 8.96 pmol/l, p<0.05).
- People with Stage 5 CKD (N=111, mean iPTH 24.29 pmol/l) had significantly higher serum iPTH than people with Stage 4 CKD (N=354, mean iPTH 16.47 pmol/l, p<0.05).

Serum Vitamin D: There were NS changes across all stages of CKD for serum 25 (OH) D_3 (N=205).

- Serum 1, 25 OH_2 D_3 (N=522) remained stable from Stages 1 to 2 and then decreased thereafter.
- People with Stage 3 CKD (N=221, mean 1, 25 OH_2 D_3 25.7 pg/ml) had significantly lower levels of mean serum 1, 25 OH_2 D_3 than people with Stage 2 CKD (N=87, mean 1, 25 OH_2 D_3 33.9 pg/ml, p<0.05).
- People with Stage 4 CKD (N=156, mean 1, 25 OH_2 D_3 16.8 pg/ml) had significantly lower levels of mean serum 1, 25 OH_2 D_3 than people with Stage 3 CKD (N=221, mean 1, 25 OH_2 D_3 25.7 pg/ml, p<0.05).
- People with Stage 5 CKD (N=43, mean 1, 25 OH2 D3 13.2 pg/ml) had significantly lower levels of mean serum 1, 25 OH_2 D_3 than people with Stage 4 CKD (N=156, mean 1, 25 OH_2 D_3 16.8 pg/ml, p<0.05).

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors also reported that percentage of patients having all 4 metabolites (Ca, P, iPTH, and Vitamin D) within K/DOQI recommended ranges were low. Due to early elevation of iPTH and early decrease of 1.25 Vitamin D, authors suggest early treatment with calcitriol **Limitations –**X-sectional analysis shows associations, not causal relationships, CKD defined by 1 creatinine measurement, Cockcroft-Gault CrCl used to assign people to various stages of CKD (K/DOQI).								

Table 350: Ref ID: 1401 [Hsu et al. 2002]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. Nephrol Dial Transplant. 2002; 17(8):1419-1425. Ref ID: 1401	Cross-sectional study NHANES III, USA Evidence Level: 3	N total =14722 N CrCl > 80 ml/min = 8425 N CrCl 70-80 ml/min = 1910 N CrCl 60-70 ml/min = 1473 N CrCl 50-60 ml/min = 1163 N CrCl 40-50 ml/min = 866 N CrCl 30-40 ml/min = 614 N CrCl 20-30 ml/min = 224 N CrCl < 20	**Inclusion criteria:** a general health survey was conducted in USA in 1988-1994 of non-institutionalised adults 20 years or older. Random selection using a stratified cluster method. Analysis restricted to adults > 17 years who had a serum creatinine, Na, K, bicarbonate, ionised Ca, phosphorus, and albumin measurement. **Exclusion criteria:** hemophilia, recent cancer chemotherapy **Baseline Characteristics:** 47% male, 41% non-Hispanic white, 29% non-Hispanic black, Mean CrCl 85 ml/min (female), 90 ml/min (male), mean serum P 3.5 mg/dl (female) and 3.4 mg/dl (male), mean ionised Ca (normalised) 1.24 mmol/l (female) and 1.24 mmol/l (male)	Serum P and Ca levels in people with decreasing deciles of CrCl stratified by gender **Procedure:** 24-h dietary recall and medication use assessed through patient interviews. Participants asked to fast for at least 6 h prior to phlebotomy. Serum total Ca, P, creatinine analysed with autoanalyser. Ionised Ca measure was normalised for serum pH. Cockcroft Gault equation used to estimate creatinine clearance (CrCl). The laboratory normal reference range for ionised Ca was 1.13-1.32 mmol/l. The laboratory normal reference range for serum P was 2.7-4.5 mg/dl. Upper limit of	Serum P and Ca levels in people with CrCl > 80 ml/min stratified by gender.	N/A	Serum P Serum Ca	NIH

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
		ml/min = 47		laboratory normal reference for serum P was > 4.5 mg/dl.				

Effect size: Focus of the paper is on changes in serum P and Ca.

CrCl and serum P:

In both men and women, serum P increased with decreasing CrCl.

Compared with women with CrCl > 80 ml/min (N=4078) significant increases in serum P were observed in women with CrCl 50-60 ml/min (N=697, change in serum P= 0.1 mg/dl (95% CI 0.1 to 0.2), p <0.0001). This trend of increasing P continued with decreasing CrCl (change in P = 0.2 mg/dl in CrCl 30-40, p<0.0001; 0.3 mg/dl in CrCl 20-30 ml/min, p=0.0003; 0.8 mg/dl in CrCl < 20 ml/min, p=0.002)

CrCl (ml/min)	N total	% hyperphosphataemia (95% CI) - serum P > 4.5 mg/dl
> 40	Not stated	≤ 2 (95% CI not given)
30-40	614	3 (1 to 6%)
20-30	224	7 (1 to 12%)
≤ 20	47	30 (0 to 62%)

CrCl and serum ionised Ca++:

Compared to people with CrCl > 80 ml/min, there were NS changes in ionised Ca with declining CrCl. Compared to men with CrCl > 80 ml/min (N=4347), men with CrCl < 20 ml/min (N=20) had a significant decrease in ionised serum Ca [change in ionised Ca = -0.03 mmol/l (95% CI -0.05 to -0.01), p=0.002].

Serum total Ca or serum total Ca adjusted for albumin levels were not lower at lower CrCl (data not shown).

Note: Limitations –X-sectional analysis shows associations, not causal relationships and no longitudinal follow-up, CrCl defined by 1 creatinine measurement, no PTH or vitamin D measures, serum biochemistry performed only once.

Table 351: Ref ID: 235 [LaClair et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
LaClair RE, Hellman RN, Karp SL et al. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States.[see comment]. American Journal of Kidney Diseases. 2005; 45(6):1026-1033. Ref ID: 235	Cross-sectional study 12 centres, USA Evidence Level: 3	N total =201 N Stage 3 GFR 30-60 ml/min = 65 N Stage 4 GFR 15-30 ml/min = 113 N Stage 5 GFR < 15 ml/min = 22	**Inclusion criteria:** people > 18 years old with known CKD and GFR 15-59 ml/min **Exclusion criteria:** RRT, proteinuria > 5g/24-h, poorly controlled hypertension, diabetes, or vasculitis, use of vitamin D or phosphate binders **Baseline Characteristics:** Mean GFR 27 ml/min, mean age 65 years, 65% male	Serum parameters in Stage 4 N= 113 Serum parameters in Stage 5 N= 22 **Procedure:** GFR was measured with Cockcroft-Gault equation. Serum 1, 25 OH_2 D_3 (Nichols radioimmunoassay, reference range 15-62 pg/ml) and 25 (OH) D_3 (Nichols Advantage chemiluminescence, reference range 10-68 ng/ml), iPTH (Nichols Advantage chemiluminescence, reference range 10-65 pg/ml, Ca (corrected for albumin), P, creatinine were analysed with autoanalyser at a central laboratory.	Serum parameters in Stage 3 N= 65	N/A	Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH_2 D_3) Serum 25-hydroxyvitamin D [25 (OH) D_3]	Genzyme Inc.
Effect size **GFR and serum Ca:** People with Stage 4 CKD (N=113, mean Ca 2.30 mmol/l) or Stage 5 CKD (N=22, mean Ca 2.25 mmol/l) had significantly lower serum Ca than people with Stage 3 CKD (N=65, mean Ca 2.37 mmol/l, p not stated). 43% of people with Stage 3 CKD (N=65) and 71% of people with Stage 4 CKD (N=113) had serum Ca < 2.37 mmol/l.								

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

GFR and serum P:

People with Stage 4 CKD (N=113, mean P 1.32 mmol/l) or Stage 5 CKD (N=22, mean P 1.42 mmol/l) had significantly higher serum P than people with Stage 3 CKD (N=65, mean P 1.13 mmol/l, p not stated).

3% of people with Stage 3 CKD (N=65) and 22% of people with Stage 4 CKD (N=113) had serum P > 1.52 mmol/l.

GFR and serum iPTH:

People with Stage 4 CKD (N=113, mean iPTH 235 pg/ml) or Stage 5 CKD (N=22, mean iPTH 310 pg/ml) had significantly higher serum iPTH than people with Stage 3 CKD (N=65, mean iPTH 114 pg/ml, p not stated).

Only 35% of people with Stage 3 (N=65) and 31% of people with Stage 4 CKD (N=113) had iPTH within K/DOQI target range (< 70 Stage 3, < 110 Stage 4)

GFR and serum 25 (OH) D_3

People with Stage 4 CKD (N=113, mean 25 (OH) D_3 46.4 nmol/l) or Stage 5 CKD (N=22, mean 25 (OH) D_3 29.9 nmol/l) had lower serum 25 (OH) D_3 than people with Stage 3 CKD (N=65, mean 25 (OH) D_3 58.2 nmol/l, p not stated). No discussion of the significance of this result.

57% of people with Stage 3 CKD (N=65) and 58% of people with Stage 4 CKD (N=113) had 25 (OH) D_3 insufficiency (25 (OH) D_3 10-30 ng/ml).

14% of people with Stage 3 CKD (N=65) and 26% of people with Stage 4 CKD (N=113) had 25 (OH) D_3 deficiency (25 (OH) D_3 < 10 ng/ml).

GFR and serum 1, 25 OH_2 D_3

People with Stage 4 CKD (N=108, mean 1, 25 OH_2 D_3 62.3 pmol/l) or Stage 5 CKD (N=20, mean 1, 25 OH_2 D_3 54.3 pmol/l) had significantly lower serum 1, 25 OH_2 D_3 than people with Stage 3 CKD (N=63, mean 1, 25 OH_2 D_3 79.6 pmol/l, p not stated).

Limitations – population is older people, X-sectional analysis shows associations, not causal relationships

Table 352: Ref ID: 3982 [Levin et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Levin A, Bakris GL, Molitch M et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007; 71(1):31-38. Ref ID: 3982	Cross-sectional study Baseline analysis of SEEK 153 centres, USA Evidence Level: 3	N total =1814 N GFR > 60 ml/min = 408 N GFR 59-30 ml/min = 1109 N GFR < 30 ml/min = 297	**Inclusion criteria:** Study for the Evaluation of Early Kidney disease (SEEK) participants:> 40 years old, MDRD eGFR < 60 ml/min **Exclusion criteria:** RRT, history of primary parathyroid disease, use of any prescription-based vitamin D therapy 12 months prior to screening **Baseline Characteristics:** Mean GFR 47 ml/min, 85% hypertensive, 71% > 65 years old, mean age 70 years, 35% CAD, 47% diabetic, 12% African American, 48% male, 25% receiving Ca supplementation, 8.7& hormone replacement therapy, 8% receiving bisphosphonates, 38% ACE inhibitors use, 34% ARB	N/A **Procedure:** Participant charts screened for serum creatinine in 2003-04 to determine eligibility for inclusion in the study. Medical history, medications, blood and urine samples collected at baseline (June 2004 to October 2004). Serum 1, 25 OH_2 D_3 and 25 (OH) D_3 determined with DiaSorin radioimmunoassay. Serum Ca, P, creatinine analysed with autoanalyser. Total Ca was corrected for serum albumin. Serum iPTH determined by chemiluminescence assay. Lab references 10-65 pg/ml for iPTH, 8-60 ng/ml for 25 (OH) D_3 and 25-65 pg/ml for 1, 25 OH_2 D_3. Dietary supplementation of vitamin D and multivitamin intake	N/A	N/A (Baseline analysis)	Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH_2 D_3) Serum 25-hydroxyvitamin D [25 (OH) D_3]	Abbott Pharmaceuticals

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			use, 64% diuretic use	up to 400 IU/day permitted.				

Effect size:

Discrepancy between screening serum creatinine and baseline creatinine measurement resulted in some people with eGFR > 60 ml/min being included in the study (N=408)

GFR and serum P and Ca:

Median Ca and P levels remained stable and within normal levels across GFR (patients stratified by decile GFR). P levels increased at GFR < 20 ml/min. Of people with eGFR 20-29 ml/min (N=204), 15% had abnormal phosphorus levels (P > 4.6 mg/dl). Of people with GFR < 20 ml/min (N=93) 40% had abnormal phosphorus levels (P > 4.6 mg/dl). (Note that original Levin et al. paper stated abnormal P levels as P < 4.6 mg/dl. EC and PS think this was a misprint and should be P > 4.6 mg/dl).

Of people with eGFR 20-29 ml/min (N=204), < 10 % had abnormal Ca levels (Ca < 8.4 mg/dl). Of people with GFR < 20 ml/min (N=93) 15% had abnormal Ca levels (Ca < 8.4 mg/dl).

GFR and serum iPTH: iPTH levels were relatively stable until GFR decreased to 45 ml/min.

eGFR (ml/min/1.73 m^2)	N	Prevalence (%) Hyperparathyroidism (iPTH > 65 ng/ml)
> 80	61	12
70-79	117	17
60-69	230	21
59-50	396	* 30
49-40	355	* 40
39-30	358	* 55
29-20	204	* 70
< 20	93	* 85

*EC estimated from Figure 4

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding

GFR and serum Vitamin D: 1, 25 OH_2 D_3 and 25 (OH) D_3

Both levels of 1, 25 OH_2 D_3 and 25 (OH) D_3 decreased with decreasing eGFR. The decrease in 1, 25 OH_2 D_3 was more rapid than the decrease in 25 (OH) D_3 . Multiple regression analysis showed a relationship between eGFR and 1, 25 OH_2 D_3 (R2 = 0.3827, p < 0.0001) but not between eGFR and 25 OH D_3 (p=0.8932). Deficiency of 1, 25 OH_2 D_3 was seen as GFR decreased to approx. 45 ml/min/1.73 m^2 (about the GFR as iPTH levels approached hyperparathyroidism levels). The prevalence of deficiency in 25 OH D_3 (25 OH D_3 < 15 ng/ml) remained stable until GFR < 30 ml/min, when the prevalence of 25 OH D_3 deficiency increased.

eGFR (ml/min/1.73 m^2)	N	** Prevalence (%) 1, 25 OH_2 D_3 deficiency (1, 25 OH_2 D_3 < 22 pg/ml)	** Prevalence (%) 25 OH D_3 deficiency (25 OH D_3 < 15 ng/ml)
> 80	61	12	10
70-79	117	15	10
60-69	230	15	5
59-50	396	20	5
49-40	355	30	15
39-30	358	45	15
29-20	204	50	20
< 20	93	65	25

** EC estimated from Figure 6.

49% of people with low 1, 25 OH_2 D_3 levels had high iPTH (irrespective of 25 OH D_3 levels), whereas 35% of those with low 25 OH D_3 levels had high iPTH levels (p<0.05).

Multivariate analysis (adjusted for age, gender, race, GFR, diabetes, urinary ACR, Ca, P):

Diabetes, decreased GFR, and increased urinary ACR independently predicted low 1, 25 OH_2 D_3.

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Note: Limitations – population is older people, X-sectional analysis shows associations, not causal relationships, CKD defined by 1 creatinine measurement								

Table 353: Ref ID: 1811 [St.John et al. 1992]

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
St John A., Thomas MB, Davies CP et al. Determinants of intact parathyroid hormone and free 1,25-dihydroxyvitamin D levels in mild and moderate renal failure. Nephron. 1992; 61(4):422-427. Ref ID: 1811	Observational study 2 nephrology clinics, Australia Evidence Level: 3	N total =51 N mild CRF (GFR 40-90 ml/min/1.73 m^2) = 27 N moderate CRF (GFR 20-39 ml/min/1.73 m^2) = 12 N healthy subjects = 12	**Inclusion criteria:** patients with mild (GFR 40-90) or moderate (GFR 20-39) age 22-68 years were recruited from 2 nephrology units in July 1988-June 1989. Healthy subjects with no prior renal disease were controls. **Exclusion criteria:** patients taking prednisolone, vitamin D derivatives, high dose oral calcium, or phosphate binders **Baseline Characteristics:** Primary diagnosis of renal disease: 28% glomerulonephritis, 28% hypertensive, 15% polycystic kidney disease, 13% chronic interstitial nephritis, 8% diabetic nephropathy, 8% renal transplant donors. Mean age: 34 (healthy), 48 (mild CRF), 45 (moderate CRF). Mean GFR: 115	Serum markers of bone metabolism in people with mild renal failure (GFR 40-90 ml/min/1.73 m^2) N = 27 Serum markers of bone metabolism in people with moderate renal failure (GFR 20-39 ml/min/1.73 m^2) N = 12 **Procedure:** Following an overnight fast, GFR was determined by clearance of [^{99mTc}]DTPA from the plasma. Blood samples assayed for total Ca, P, albumin, creatinine, bicarbonate, alkaline phosphatase. Serum 1, 25 OH_2 D_3 was determined with a bovine thymus cytoreceptor assay. Serum 25 (OH) D_3 was determined using rat	Serum markers of bone metabolism in healthy people N=12	N/A	Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH_2 D_3) Serum 25-hydroxyvitamin D [25 (OH) D_3]	Telethon Foundation and Sir Charles Gairdner Hospital Research Foundation grants

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
			ml/min/1.73m^2 (healthy), 56 ml/min/1.73m^2 (mild CRF), 32 ml/min/1.73m^2 (moderate CRF)	kidney cytosol. Serum iPTH determined by an immunochemiluminometric assay.				

Effect size:

Changes in plasma iPTH and 1,25 Vit D precede changes in calcium or phosphate.

Plasma Ca:

- There were NS differences in mean Ca levels for people with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean Ca 2.31 mmol/l) compared with healthy controls (N=12, mean Ca 2.27 mmol/l).
- People with moderate CRF (GFR 20-39 ml/min/1.73m^2, N=12, mean Ca 2.24 mmol/l) had significantly lower Ca levels than people with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean Ca 2.31 mmol/l, p<0.05)

Plasma P:

- There were NS differences in mean phosphate levels for people with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean P 1.0 mmol/l) compared with healthy controls (N=12, mean P 1.1 mmol/l).
- People with moderate CRF (GFR 20-39 ml/min/1.73m^2, N=12, mean P 1.2 mmol/l) had significantly higher P levels than people with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean P 1.0 mmol/l, p<0.05)

Plasma iPTH:

- People with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean iPTH 57.5 pg/ml) had significantly higher levels of iPTH than healthy people (N=12, mean iPTH 25.4 pg/ml, p<0.05).
- People with moderate CRF (GFR 20-39 ml/min/1.73m^2, N=12, mean iPTH 139 pg/ml) had significantly higher iPTH levels than people with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean iPTH 57.5 pg/ml, p<0.05)
- People with moderate CRF (GFR 20-39 ml/min/1.73m^2, N=12, mean iPTH 139 pg/ml) had significantly higher iPTH levels than healthy people (N=12, mean iPTH 25.4 pg/ml, p<0.05).

Reference	Study type	Number of patients	Patient characteristics	Intervention/ exposure	Comparison	Length of follow-up	Outcome measures	Source of funding
Note that 17/39 (44%) people with CRF were still within the reference range of iPTH (even at low GFR). The increase in iPTH above reference values began at GFR < 60 ml/min/1.73m^2. **Plasma Vitamin D:** • People with mild CRF (GFR 40-90 ml/min/1.73m^2, N=27, mean 1, 25 OH_2 D_3 = 42.1 pg/ml) had significantly lower levels of 1, 25 OH_2 D_3 compared with healthy people (N=12, mean 1, 25 OH_2 D_3 = 54.6 pg/ml, p<0.05). • People with moderate CRF (GFR 20-39 ml/min/1.73m^2, N=12, mean 1, 25 OH_2 D_3 = 39.2 pg/ml) had significantly lower levels of 1, 25 OH_2 D_3 compared with healthy people (N=12, mean 1, 25 OH_2 D_3 = 54.6 pg/ml, p<0.05). Note than 9/39 (23%) people with CRF were BELOW the reference range of 1, 25 OH_2 D_3. This occurred at GFR < 60 ml/min/1.73m^2. There were NS differences in 25 (OH) D_3. **Note:** – accurate measure of GFR used, but in small number of patients. Observational study.								

Q.5.14 Risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD (2014 guideline – chapter 13.2)

Table 354: Ref ID: 3990 [Jamal et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M,	RCT Evidence level: 1+	N=6458 N=2027 in the	**Inclusion criteria:** women were enrolled in FIT if they were 55-80 years old, at least 2 years postmenopausal, femoral neck BMD ≤0.68 g/cm^2.	Alendronate (dose not mentioned in this paper)	Placebo	48 months in the clinical fracture arm	BMD Fractures: Clinical	Canadian Institutes of Health Research

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ishani A, Cummings SR. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. Journal of Bone and Mineral Research 2007; 22 (4): 503-508	Secondary analysis of an RCT [Fracture Intervention Trial (FIT)]	vertebral fracture arm N=4432 in the clinical fracture arm	**Exclusion criteria**: serum creatinine >1.27 mg/dl, serum PTH >85 pg/ml in isolation or serum PTH > 65 pg/ml in combination with abnormal serum calcium, alkaline phosphatase or phosphate. **Baseline characteristics:**	**Protocol:** Bone mineral density (BMD) measured on whole body, femoral neck, total hip and lumbar spine using DXA. eGFR calculated by Cockroft-Gault formula. eGFR<45 ml/min was considered severely reduced renal function; eGFR 45-59 ml/min moderately reduced renal function; eGFR ≥ 60 ml/min normal renal function. Incident vertebral fractures assessed by blinded radiologists.		36 months in the vertebral fracture arm	fractures as reported by patients (assessment by blinded radiologist) Radiographic vertebral fractures: identified by morphometric and semi-quantitative techniques Adverse events	

	eGFR <45	eGFR ≥45	p
N	581	5877	
Age (y)	74.6 (4.4)	68.1 (6.0)	<0.00001
Weight (kg)	52.9 (6.7)	65.7 (10.7)	<0.00001
BMI (kg/m^2)	21.8 (2.6)	25.5 (4.0)	<0.00001
Total hip BMD (g/cm^2)	0.63 (0.1)	0.70 (0.1)	<0.00001
Femoral neck BMD (g/cm^2)	0.54 (0.1)	0.59 (0.1)	<0.00001
Lumbar spine BMD (g/cm^2)	0.78 (0.2)	0.83 (0.1)	<0.00001
% Vertebral fracture	42.2	30.3	<0.00001
ALP (U/l)	83.3	85.7	0.0064

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				(20.0)	(20.3)		Blood chemistry (Ca, P, creatinine, ALP, PTH) measured at baseline and annually. Adverse events assessed over the phone or at clinic visits every 3 months.				
			% Fracture after age 45	46.9	41.7	0.02					

Effect size:

Standard WHO definition of osteoporosis used: BMD at femoral neck, total hip or lumbar spine of ≤ 2.5 SD below mean BMD for young adult women (T score of ≤ -2.5); T score between -1 and -2.5 classified as osteopenia; T score >-1 classified as 'normal BMD'.

Ch**ange in BMD [%change (95%CI)], alendronate vs. placebo, by eGFR**

	All women	Severely reduced eGFR (eGFR<45)	Moderately reduced or normal eGFR (eGFR ≥45)	P for interaction
All women (N=6458)				
Total hip	4.9 ± 8.7%	5.6 (4.8-6.5)	4.8 (4.6-5.0)	0.04
Femoral neck		5.0 (4.0-5.9)	4.5 (4.2-4.8)	0.32
Spine	6.6 ± 5.8%	6.7 (5.7-7.8)	6.6 (6.3-6.9)	0.75
Women with osteoporosis (N=3214)				
Total hip		4.9 (3.7-6.3)	4.7 (4.4-5.0)	0.61
Femoral neck		4.5 (3.2-5.8)	4.2 (3.8-4.7)	0.73
Spine		5.9 (4.3-7.5)	6.4 (6.2-7.1)	0.33

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Fracture risk [Odds ratio (95%CI)], alendronate vs. placebo, by eGFR				
	All women	Severely reduced eGFR	Moderately reduced or normal eGFR	P for interaction	Risk of fracture in women with eGFR<45 vs. eGFR≥45
All women (N=6458)					
Clinical fractures	0.8 (0.7-0.9)	0.78 (0.51-1.2)	0.81 (0.70-0.94)	0.90	1.3 (1.0-1.6)
Spine fractures	0.54 (0.37-0.78)	0.72 (0.31-1.7)	0.50 (0.32-0.76)	0.44	2.5 (1.6-3.9)
Women with osteoporosis (N=3214)					
Clinical fractures		0.84 (0.45-1.54)	0.74 (0.61-0.91)	0.72	
Spine fractures		1.01 (0.29-3.6)	0.62 (0.36-1.10)	0.49	

Serum creatinine: there was an increase in serum creatinine that was the same in those with and without reduced renal function (mean increase in both groups: 0.01 ± 0.10; p=0.88); and was the same in the placebo and alendronate treated groups (mean increase: 0.01 ± 0.10; p=0.99)

Adverse events

NS differences in adverse events experienced by people with severe renal dysfunction or reduced/normal renal function.

Frequency of reported adverse events	Severely reduced eGFR	Moderately reduced or normal eGFR	p
Overall (%)	99.1	99.5	0.189
Gastrointestinal events (%)	4.5	5.2	0.5
Cerebrovascular (%)	2.2	2.2	0.9
Cardiovascular (%)	2.6	3.2	0.4
Arrhythmias (%)	2.4	2.1	0.7
Malignancies (%)	4.3	5.0	0.4
Death (%)	1.6	1.9	0.5

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Renal adverse events (%)			2.1	2.3	0.68			
Conclusions: oral bisphosphonates are effective at increasing BMD and decreasing fracture risk and are not associated with an increase in serum creatinine, reduction in creatinine clearance, or an increase in adverse events. **Assessment of bias:** RCT details of which are not mentioned in this paper, no mention of ITT, method of randomisation, concealment. Assessors of radiographic evidence were blinded. This was a post-hoc analysis.								

Table 355: Ref ID: 3991 [Kikuchi et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kikuchi Y, Imakiire T, Yamada M, Saigusa T, Hyodo T, Kushiyama T, Higashi K, Hyodo N, Yamamoto K, Suzuki S, Miura S. Effect of risedronate on high-dose corticosteroid-induced bone loss in patients with glomerular disease. Nephrol Dial Transplant 2007; 22: 1593-1600	RCT Evidence level: 1+ Randomised, open-label, prospective study Randomisation using envelope randomisation method. ITT	N =38 Drop out rate 0% Japanese population	Inclusion criteria: patients with glomerulonephritis initiating high-dose corticosteroid therapy (>30 mg/day prednisolone, including steroid pulse therapy Exclusion criteria: severe renal dysfunction due to rapidly progressive glomerulonephritis, very high (>130%) or very low (<80%) BMD Baseline characteristics: There were NS differences in sex, age, BMI, BMD or the biochemical markers of bone metabolism among the groups. Mean GFR was 78 ml/min (Group R), 74 ml/min (Group R + A), 81 ml/min (Group A)	N=12 Group R: risedronate 2.5mg/day N=15 Group A: alfacalcidol 0.5 µg/day (an active vitamin D3 analogue) Procedure: Patients randomised to risedronate alone, alfacalcidol alone, or risedronate + alfacalcidol. Drugs were simultaneously started with the initiation of steroid therapy. No patients received Ca supplementation. BMD (assessed by DEXA) measured at baseline and 12 months following randomisation. CrCl calculated (method not	N=11 Group R+A: risedronate 2.5mg/day and alfacalcidol 0.5 µg/day	1 year	BMD GFR Urinary protein Serum blood urea nitrogen and creatinine (BUN) ALP iPTH osteocalcin urinary cross-linked N-telopeptide of type I collage (NTx)	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Urinary protein was higher in the R+A group than in group R or A, but this was not significant.	stated).				
Effect size: **BMD Changes**								
		Group R		**Group R+A**		**Group A**		
BMD baseline (g/cm^2)		1.04 ± 0.10		1.06 ± 0.11		1.02 ± 0.10		
BMD at 12 months (g/cm^2)		1.03 (NS change from baseline)		1.08 (p<0.05 from baseline)		0.96 (p<0.05 from baseline) [p=0.001 compared to R+A)		
Adverse Events: No patients were excluded due to adverse events and no list of adverse events given. **Fractures:** There were no fractures that occurred in the study. Several factors (osteocalcin, ALP, urinary NTx, iPTH) showed significant changes from baseline; but NS significant differences between the groups. **Predictive factors for loss of BMD:** patients were classified into 3 groups on the basis of BMD change and predictive factors for BMD loss were assessed (Group I BMD increase >1.1% (N=12); Group II mild change in BMD -3.2 to +1.1% (N=13); Group III BMD decreased > 3.2% (N=13)). There were no significant differences in sex, age, BMI, BMD or renal function at baseline among the groups. Urinary NTx was significantly higher in groups II and III than in group I. Serum osteocalcin, ALP also higher in Groups II and III than I, but NS. **Assessment of bias:** ITT analysis, no drop outs, open-label study, small numbers.								

Table 356: Ref ID: 3987 [Miller et al. 2005]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. Journal of	Meta-analysis Evidence level : 1+ Data from 9 randomised, double blind, placebo controlled, parallel group phase III trials were included, all used risedronate for the	N=9883 Dropout rate: 36% in placebo group and 35% in risedronate group	**Inclusion criteria:** inclusion criteria of different studies not mentioned. Population is osteoporotic women with renal disease. **Exclusion criteria:** patients were excluded from the individual studies if they had evidence of clinically significant systemic disease such as history of hyperparathyroidism, hyperthyroidism or osteomalacia within 1 year before enrolment; or markedly abnormal lab values including serum creatinine levels >1.1 times the ULN. **Baseline characteristics:** within each renal impairment subgroup, the 2 treatment groups (placebo and risedronate) were very similar with respect to baseline demographic and disease characteristics. Risedronate / Placebo N: 4500 / 4496 Age (yrs): 75 (80) / 75 (8.2)	Risedronate (5 mg daily) N= 4496 overall N Severe CKD=301 N moderate CKD = 2034 N mild CKD = 2161 **Protocol:** Analysis of trials stratified by renal function: mild (CrCl >50 to 80 ml/min), moderate (CrCl >30 to <50 ml/min) or severe (CrCl <30 ml/min) renal impairment. BMD (assessed with DXA) measured at baseline, at 6, 12, 24 months and at endpoint. Vertebral	Placebo N=4500 overall N Severe CKD=271 N moderate CKD = 2037 N mild CKD = 2192	Average duration of treatment 2 years.	Primary outcome: safety. Adverse events Secondary outcomes: efficacy BMD (measured by DXA) Creatinine clearance (CrCl)	Procter & Gamble pharmaceuticals (USA), Sanofi-Aventis (USA)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bone and Mineral Research 2005; 20(12): 2105-2115	treatment of osteoporosis.		Serum creatinine mg/dl	0.98 (0.208)	0.99 (0.22)	fractures (decrease of 15% or more in vertebral height or a change from grade 0 to grade 1 or more) assessed by blinded radiologists.				
			CrCl ml/min	49.5	49.2					

Effect size:

Of the 9883 women on the database 91% (8996/9883) had some degree of renal impairment. Severe 572/9883 (5.8%), moderate 4071/9883(41.2%) and mild 4353/9883 (44.0%).

Adverse events: The incidence of overall, urinary and renal function related adverse events were similar within and between treatment groups in the subgroups of patients with severe, moderate and mild renal impairment. Statistically and clinically there were NS differences.

Changes in serum creatinine: There were NS differences between the placebo and risedronate groups in changes from baseline in serum creatinine in any of the renal impairment groups.

BMD:

	Placebo vs.risedronate in mild renal impairment	Placebo vs.risedronate in moderate renal impairment	Placebo vs.risedronate in severe renal impairment
Mean % change (SE) in lumbar spine BMD	-0.14% (0.19%) vs.3.96% (0.18%); p<0.001	-0.47% (0.50%) vs.4.33 (0.51%); p<0.001	-1.37% (1.72%) vs.4.23% (1.82%); p<0.001

The mean percent increase from baseline to endpoint in BMD at the femoral neck and trochanter was significantly greater in the risedronate 5 mg group than in the placebo group in all 3 renal impairment subgroups, except at the femoral neck in the severe renal impairment subgroup.

Incidence of new vertebral fractures: Incidence of new vertebral factures was significantly lower in the risedronate group than the placebo groups within each renal impairment subgroup. Within the risedronate treatment group, the incidence of new vertebral fractures was similar across renal impairment subgroups (p=0.124). The

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
incidence in the placebo treated group increased significantly with the severity of renal impairments (p<0.001). [Note that Figure 2 was very difficult to interpret. Looks as if 56% of placebo and 12% of risedronate group had new fractures in the severe CKD group. Is this reasonable?] **Assessment of bias:** posthoc analysis of pooled data from 9 trials, ITT analysis, all trials reported to be randomised and double blind but no details of each given.								

Table 357: Ref ID: 3979 [Fuji et al. 2007]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fujii N, Hamano T, Mikami S, Nagasawa Y, Isaka Y, Moriyama T, Horio M, Imai E, Hori M, Ito T. Risedronate, an effective treatment for glucocorticoid – induced bone loss in CKD patients with or without concomitant active vitamin D (PRIUS-CKD) Nephrol Dial Transplant 2007; 22: 1601-1607	RCT Evidence level 1- Poorly randomised, prospective, open-label, study Per-protocol analysis Randomisation using computer software	N=114 19.2% (15/78) of patients taking risedronate withdrew	**Inclusion criteria:** CKD outpatients receiving glucocorticoid therapy (prednisone equivalent of ≥2.5 mg/day) for >6 months **Exclusion criteria:** current treatment with bisphosphonate, native Vit D, oestrogen, selective oestrogen receptor modulator (SERM), or human parathyroid hormone, any concurrent diseases that affect bone turnover such as primary hyperparathyroidism and thyroid dysfunction, kidney transplant patients and females planning pregnancy. **Baseline characteristics:** Mean age (SD) 42.5 ±	Group A: Active Vit D alone N=38 Group B: Active Vit D + risedronate 2.5 mg/day (randomisation conducted so that this group had 40% more patients than group A) N=50 **Protocol:** Subjects randomised to Vitamin D alone (Group A), Vitamin D + risedronate (Group B). Remainder allocated to risedronate alone (Group C). Diuretic, Ca supplement, beta blocker, vitamin D use not changed during study. BMD of the second to fourth lumbar vertebrae measured every 6 months and blood chemistry at baseline, 1, 3, and 6	Group C: Risedronate 2.5 mg/day N=26	1 year	Bone mineral density (BMD) Creatinine clearance (CrCl) Serum N-terminal telopeptides of type I collagen (S-NTX) [a marker for bone turnover] Bone ALP	In part by Sanofi-Aventis (Tokyo, Japan)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			16.6 years Sex Male 47% (54/114) CrCl (SD) 99.6 ± 35.8 ml/min/1.73m^2	months, after randomisation measured using a dual-energy X-ray absorptiometer. CrCl estimated using the Cockcroft-Gault formula.				

Effect size

	Group A (Vitamin D alone)	Group B (Vitamin D + Risedronate)	Group C (Risedronate alone)
Change in BMD Lumbar spine at 12 months	-1.2 ± 0.6% NS, no p-value given	+2.8 ± 1.3% Significant, no p-value given	+2.1 ± 1.0% Significant, no p-value given
Change in S-NTX at 6 months	+4.7% (p<0.05 compared to B)	-19.6% (p<0.01 for change from baseline)	-14.6% (p<0.05 for change from baseline)
Change in bone ALP at 6 months	+26.9% (p<0.05 compared to B or C)	-11.6%	-10%

- Changes in BMD at the femoral neck were not obvious in any group.
- There was a mild tendency of a stepwise increase in the lumbar BMD with the greater reduction in S-NTX at 6-months (but not statistically significant).
- Baseline values of bone turnover markers were not associated with percentage changes in lumbar BMD after 1 year of risedronate treatment.
- Changes in CrCl were similar across all groups.

Assessment of bias: only the patients in the active Vit D group were randomised, patients in group C were allocated to risedronate without any form of randomisation. Per-protocol analysis. Open-labelled study.

Conclusions: monotherapy with active vitamin D fails to maintain the bone mass of CKD patients receiving glucocorticoids. Risedronate with or without vitamin D is an effective treatment for glucocorticoid induced bone loss in CKD patients in terms of BMD.

Caution: 2.5 mg risedronate below recommended dose for treatment of osteoporosis.

Appendix R: References

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