National Institute for Health and Care Excellence

Final

# Chronic kidney disease

## [G] Evidence review for optimal blood pressure targets for adults, children and young people with CKD

*NICE guideline NG203*

*Evidence reviews underpinning recommendations 1.6.1 to 1.6.3 in the NICE guideline*

*August 2021*

*Final*

*These evidence reviews were developed by Guideline Updates Team*

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# Contents

# Optimal blood pressure ranges for adults, children and young people with chronic kidney disease

## 1.1 Review question

In adults, children and young people with CKD, what are the optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality?

### 1.1.1 Introduction

The NICE guideline on chronic kidney disease in adults: assessment and management (NICE guideline CG182) was reviewed in 2017 as part of NICE's surveillance programme. As a result of the review, the decision was made to update the guideline. During the scoping phase of the update, it was decided to extend the guideline to cover the assessment and management of chronic kidney disease in children and young people. As part of the scoping exercise, stakeholders highlighted that children and young people with CKD need a different management compared to that for adults with CKD. Stakeholders also highlighted new trials reporting evidence for the management of blood pressure control in adults with CKD.

The aim of this review is to investigate optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality in adults, children and young people with CKD. See Appendix A for full details of the review protocol.

### 1.1.2 Summary of the protocol

**Table 1: PICO table for optimal blood pressure ranges in adults, children and young people with CKD**

| | |
|---|---|
| **Population** | Adults, children and young people with suspected or diagnosed chronic kidney disease GFR categories G1 to G5. |
| **Intervention** | 'Intense' or 'strict' blood pressure control (as defined by the author), including both drug and lifestyle interventions. |
| **Comparator** | 'Normal' management of BP (as defined by author), including any variation data, for example change from baseline. |
| **Outcomes** | • All-cause mortality<br>• Cardiovascular mortality and morbidity<br>• Heart failure<br>• Decline in eGFR or creatinine clearance<br>• Progression to ESRD or ESKD<br>• % of people reaching target BP<br>• Adverse events:<br>  ○ falls/fractures<br>  ○ postural hypotension<br>  ○ electrolyte disorders<br><br>Similar time-points will be grouped for analysis.<br>Results will be stratified by diabetic and non-diabetic populations. |

### 1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

Methods specific to this review:

a) The committee requested additional evidence to be presented that was not included in the protocol. The evidence they requested was on composite outcomes reported by the studies, and on proteinuria. The additional evidence can be found in Appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

### 1.1.4 Effectiveness evidence

#### 1.1.4.1 Included studies

A systematic search was carried out to identify RCTs and systematic reviews of RCTs, which found 4,355 references (see Appendix C for the literature search strategy). After screening at title and abstract level, 4,309 references were excluded. Full texts were ordered to be screened for 46 references. In total, 21 references were included based on their relevance to the review protocol Appendix A. Of these studies, 11 were primary studies and 10 studies were post-hoc analysis of primary studies which included additional outcomes. The clinical evidence study selection is presented as a PRISMA diagram in Appendix A.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 333 references for this review question, these were screened on title and abstract. Eight references were ordered for full text screening. Three references were included based on its relevance to the review protocol (Appendix A).

See section 1.1.10 References – included studies for a list of references for included studies.

#### 1.1.4.2 Excluded studies

See Appendix K for a list of excluded studies with the primary reason for exclusion.

### 1.1.5 Summary of studies included in the effectiveness evidence

Table 2 shows a summary of included studies with references to post-hoc publications.

**Table 2: Summary of included studies**

| Study | Population (N) | Interventions | Outcomes (Follow up) |
|---|---|---|---|
| AASK 2002 (Wright 2002) Post-hoc publication: Ku 2017 | African Americans, baseline eGFR 20 - 60 ml/min/1.73 $m^2$ (N=1,094) | Low MAP (92mmHg or less) versus standard MAP (102 - 107 mmHg) | Decline in eGFR, Decline in ESRD, mortality (3 – 6 years) |
| ACCORD 2016 (Papademetriou 2016) | Type 2 diabetes, CKD 1 to 3 (4 and 5 excluded) (N=1,726) | <120 mm Hg versus < 140 | CVD morbidity: non-fatal MI, stroke, major coronary, any chronic heart failure. CVD mortality (Mean=3.5 years) |

| Study | Population (N) | Interventions | Outcomes (Follow up) |
|---|---|---|---|
| ESCAPE 2004 (Wuhl 2004) Post-hoc publication: ESCAPE trial group 2009 | Children (3-18 years), eGFR 11-18 ml/min/1.73 $m^2$ (N=385 at randomisation) | <50th percentile of 24-hour mean arterial pressure versus 50th to 90th percentile of 24-hour mean arterial pressure | Decline in eGFR (5 years) |
| JATOS 2010 (Hayashi 2010) | Elderly (65-85 years), GFR in both groups at baseline mean approximately 60 ml/min/1.73 $m^2$ (N=2,499) | <140 mmHg versus 140 – 160 systolic blood pressure | Decline in eGFR (2 years) |
| MDRD 1994 (Klahr 1994) Post-hoc publications: Hebert 1997 Lazarus 1997 Perterson 1995 Sarnak 2005 | Adults, baseline eGFR GFR 25 to 55 ml/min/1.73 $m^2$ (N=585) | Undefined intensive versus standard | Decline in eGFR, creatine clearance, outcomes per subgroup by race (2.2 years mean) |
| REIN-2 2005 (Ruggenenti 2005) | Non-diabetic nephropathy, mean GFR approximately 35 ml/min/1.73 $m^2$ in both groups (N=335) | <130/80 mmHg versus diastolic <90 mmHg | Decline in eGFR, progression to ESRD, All-cause mortality, CVD outcomes, CVD mortality. Outcomes per subgroup by race (Unclear) |
| Schrier 2002 | ADPKD, creatine clearance > 30 mL/min (N=75) | <120/80 mmHg versus 135/85 to 140/90 mmHg | Mortality, progression to ESRD, change in serum creatinine (7 years) |
| Schrier 2014 | ADPKD, 15-49 years (N=558) | 120/70 to 130/80 versus 95/60 to 110/75 mmHg | Cardiovascular morbidity and mortality (5 years) |
| SPRINT 2017 (Cheung 2017) Post-hoc publications: Pajewski 2020 Sink 2018 Soliman 2020 Still 2018 Upadhya 2017 Vaduganathan 2020 Wright 2015 | CKD, approximately eGFR 50 ml/min/1.73 $m^2$ (N=2,646) | 120 mmHg versus 140 mmHg systolic blood pressure | Decline in eGFR, All-cause mortality, Cardiovascular morbidity and mortality. Outcomes per subgroup by age (median 3.26 years) |
| SPS3 2019 (Agarwal 2019) | CKD with eGFR <40 ml/min/1.73 $m^2$ , aged 30 years or over, with stroke in past 2 weeks (N= 474) | <130 mmHg versus 130–149 mmHg systolic blood pressure | All-cause mortality, Cardiovascular morbidity and mortality (48 mths) |
| Toto 1995 | Hypertensive nephrosclerosis, age 25-73 years, eGFR < 70 ml/min/1.73 $m^2$ | Diastolic 65 to 80 mmHg versus DBP 85 to 95 mmHg | Percentage decline in eGFR, ESKD, mortality (up to 5 years) |

| Study | Population (N) | Interventions | Outcomes (Follow up) |
|---|---|---|---|
| | (N=77) | | |

See Appendix E for full evidence tables.

### 1.1.6 Summary of the effectiveness evidence

The summary of the effectiveness evidence is provided in Table 3. Additional evidence relating to proteinuria and other composite outcomes are presented in Appendix L.

**Table 3: Intensive blood pressure therapy versus standard therapy**

| Outcomes | No of participants | Relative effect (95% CI) | Quality of the evidence (GRADE) | Interpretation of effect |
|---|---|---|---|---|
| Decline in eGFR [ml/min/1.73 $m^2$] (rate per year) | 2101 | MD - 0.08 (-0.55, 0.39) | Very low | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (rate per year) - Adults | 635 | MD - 0.05 (-0.69, 0.6) | Very low | Could not differentiate |
| Decline in eGFR [ml/min/1.73 $m^2$] (rate per year) - Children | 372 | MD - 1.4 (-2.81, 0.01) | Moderate | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (rate per year) - African American | 1094 | MD 0.26 (-0.21, 0.73) | Moderate | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) Follow-up: 2 to 3 years | 7808 | MD -0.56 (-1.47, 0.35) | Moderate | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) - Baseline eGFR 25-55 [ml/min/1.73 $m^2$], 3 years follow-up | 585 | MD -1.60 (-3.99, 0.79) | Low | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) - Baseline eGFR 13-24 [ml/min/1.73 $m^2$], 3 years follow-up | 255 | MD -0.50 (-1.71, 0.71) | Low | Could not differentiate |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) - African American, 3 years follow-up | 53 | MD -11.80 (-26.09, 2.49) | Low | Could not differentiate |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) - Elderly (65 years and older) at 2 yeas follow-up | 4416 | MD 0.00 (-1.85, 1.85) | Low | No meaningful difference |
| Decline in eGFR [ml/min/1.73 $m^2$] (change from baseline) - Elderly (65 years and older) at 2 yeas follow-up, eGFR < 60 ml/min/1.73 $m^2$ | 2499 | MD 0.10 (-4.27, 4.47) | Low | No meaningful difference |
| Participants with 30% or greater decline in eGFR (rate per year) (intensive versus standard therapy) | 2646 | HR 2.03 (1.42 to 2.9) | High | Clinically meaningful effect - Favours |

| Outcomes | No of participants | Relative effect (95% CI) | Quality of the evidence (GRADE) | Interpretation of effect |
|---|---|---|---|---|
| | | | | standard therapy[a] |
| Participants with 30% or greater decline in eGFR (rate per year) - (intensive versus standard therapy)<br>- People aged 80 years or older | 1167 | HR 3.41 (1.92–6.06) | High | Clinically meaningful effect - Favours standard therapy |
| Participants with 50% or greater decline in eGFR [ml/min/1.73 $m^2$] (rate per year) - (intensive versus standard therapy) | 2646 | HR 0.9 (0.44 to 1.84) | Moderate | Could not differentiate |
| Decline in serum creatinine [ml/min] (rate per year) Follow-up: 5 years | 77 | MD 0.05 (-0.06, 0.16) | High | Could not differentiate |
| Elevated serum creatinine, 0.3 mg per decilitre or more (acute kidney injury) | 558 | RR 1.28 (0.63 to 2.6) | Very low | Could not differentiate |
| Doubling of serum creatinine [ml/min] or ESRD - Elderly (65 years and older), 2 years follow-up | 4418 | RR 0.89 (0.34 to 2.29) | Low | Could not differentiate |
| Doubling of serum creatinine [ml/min] or ESRD - Elderly (65 years and older) with diabetes, 2 years follow-up | 521 | RR 0.32 (0.03 to 3.1) | Very low | Could not differentiate |
| Progression to ESRD Follow-up: 7 years | 487 | RR 1.25 (0.85 to 1.82) | Moderate | Could not differentiate |
| Adverse events (all) Follow-up: mean 5 years | 10584 | RR 0.98 (0.87 to 1.09) | High | No meaningful difference |
| Adverse events (all) Follow-up: median 3.7 years<br>- People aged 80 years and older | 1167 | HR 0.92 (0.79 to 1.07) | Moderate | Could not differentiate |
| Adverse events - Electrolyte abnormalities Follow-up: mean 5 years | 2646 | RR 1.34 (0.94 to 1.91) | Moderate | Could not differentiate |
| Adverse events - Electrolyte abnormalities Follow-up: median 3.5 years<br>- People aged 80 years and older | 1167 | RR 1.14 (0.69 to 1.91) | Low | Could not differentiate |
| Adverse events - Injurious fall Follow-up: mean 5 years | 2646 | RR 0.82 (0.65 to 1.04) | Moderate | Could not differentiate |
| Adverse events - Injurious fall Follow-up: median 3.5 years<br>- People aged 80 years and older | 1167 | RR 0.92 (0.63 to 1.33) | Low | Could not differentiate |
| Adverse events - Postural hypotension without dizziness Follow-up: mean 5 years | 2646 | RR 0.99 (0.86 to 1.13) | High | No meaningful difference |

| Outcomes | No of participants | Relative effect (95% CI) | Quality of the evidence (GRADE) | Interpretation of effect |
|---|---|---|---|---|
| Adverse events - Postural hypotension with dizziness Follow-up: mean 5 years | 2646 | RR 1.03 (0.59 to 1.82) | Low | Could not differentiate |
| Adverse events - Hypotension Follow-up: median 3.5 years<br>- People aged 80 years and older | 1167 | RR 1.98 (0.90 to 4.38) | Moderate | Could not differentiate |
| Heart failure Follow-up: median 3.2 years<br>- All adults with CKD | 2646 | RR 0.78 (0.52 to 1.17) | Moderate | Could not differentiate |
| Heart failure Follow-up: median 3.2 years<br>- Adults (CKD; UACR <30 mg/g) | 1737 | RR 0.56 (0.30 to 1.06) | Moderate | Could not differentiate |
| Heart failure Follow-up: median 3.2 years<br>- Adults (CKD; UACR 30 to 300 mg/g) | 651 | RR 0.94 (0.49 to 1.80) | Low | Could not differentiate |
| Heart failure Follow-up: median 3.2 years<br>- Adults (CKD; UACR >300 mg/g) | 262 | RR 1.04 (0.41 to 2.62) | Low | Could not differentiate |
| CVD morbidity (number of people) Follow-up: 7 years | 10002 | RR 0.99 (0.77 to 1.26) | Low | Could not differentiate |
| CVD morbidity (number of people) - Myocardial infarction | 2646 | RR 0.97 (0.64 to 1.46) | Low | Could not differentiate |
| CVD morbidity (number of people) - Acute coronary syndrome | 2646 | RR 1.35 (0.62 to 2.93) | Low | Could not differentiate |
| CVD morbidity (number of people) - Intracranial haemorrhage | 474 | RR 0.37 (0.07 to 1.88) | Low | Could not differentiate |
| CVD morbidity (number of people) - Stroke | 2646 | RR 0.99 (0.58 to 1.68) | Low | Could not differentiate |
| CVD morbidity (number of people) - Recurrent stroke | 474 | RR 1.13 (0.7 to 1.84) | Low | Could not differentiate |
| CVD morbidity (number of people) - Coronary artery disease | 558 | RR 0.52 (0.05 to 5.68) | Low | Could not differentiate |
| CVD morbidity (number of people) - Arrhythmias | 558 | RR 0.26 (0.03 to 2.3) | Low | Could not differentiate |
| CVD morbidity (number of people) – Atrial fibrillation | 2192 | RR 0.98 (0.63 to 1.52) | Low | Could not differentiate |
| CVD mortality (number of people) - Adults | 2981 | RR 0.59 (0.33 to 1.03) | Moderate | Could not differentiate |
| All-cause mortality (number of people) Follow-up: 7 years | 6288 | RR 0.82 (0.67 to 1.01) | Moderate | Could not differentiate |
| All-cause mortality (number of people) - Adults | 4165 | RR 0.77 (0.6 to 0.98) | High | Clinically meaningful |

| Outcomes | No of participants | Relative effect (95% CI) | Quality of the evidence (GRADE) | Interpretation of effect |
|---|---|---|---|---|
| | | | | effect - Favours intensive therapy |
| All-cause mortality (number of people) - Children | 385 | RR 0.35 (0.01 to 8.43) | Moderate | Could not differentiate |
| All-cause mortality (number of people) - African American | 1738 | RR 0.97 (0.68 to 1.39) | Moderate | Could not differentiate |
| All-cause mortality (number of people) – People aged 80 years and older | 1167 | RR 0.74 (0.56 to 0.99) | High | Clinically meaningful effect - Favours intensive therapy |
| Chronic heart failure (rate per year) in Type 2 diabetes - Any chronic heart failure Follow-up: mean 3.5 years | 1726 | HR 0.92 (0.63 to 1.34) | Moderate | Could not differentiate |
| CVD morbidity (rate per year) in Type 2 diabetes - Non-fatal Myocardial Infarction Follow-up: mean 3.5 years | 1726 | HR 0.89 (0.63 to 1.26) | Moderate | Could not differentiate |
| CVD morbidity (rate per year) in Type 2 diabetes - Non-fatal stroke Follow-up: mean 3.5 years | 1726 | HR 0.64 (0.36 to 1.14) | Moderate | Could not differentiate |
| CVD morbidity (rate per year) in Type 2 diabetes - Any stroke Follow-up: mean 3.5 years | 1726 | HR 0.62 (0.36 to 1.07) | Moderate | Could not differentiate |
| CVD mortality (rate per year) in Type 2 diabetes Follow-up: mean 3.5 years | 1726 | HR 0.93 (0.57 to 1.52) | Moderate | Could not differentiate |
| All-cause mortality (rate per year) in Type 2 diabetes Follow-up: mean 3.5 years | 1726 | HR 0.86 (0.63 to 1.17) | Moderate | Could not differentiate |

*(a) Higher rate of eGFR decline in intensive group due to the acute (up to 6 months) effect of the intervention. eGFR results from 6 months onwards showed no difference when compared to standard treatment*
*Abbreviations: CVD: cardiovascular disease, ESRD: end-stage renal disease, HR: hazard ratio, MID: minimal important difference, MD: mean difference, RR: risk ratio*

See Appendix G for full GRADE tables.

### 1.1.7 Economic evidence

A systematic review was conducted to identify economic evaluations for this review question. The search returned 2,494 records which were sifted against the review protocol. All records were excluded based on title and abstract. The study selection diagram is presented in Appendix H. For more information on the search strategy please see Appendix C.

No published cost-effectiveness studies were included in this review and this question was not prioritised for de novo economic modelling.

### 1.1.8 The committee's discussion and interpretation of the evidence

#### 1.1.8.1. The outcomes that matter most

The committee took into account all outcomes when making recommendations. The committee noted that long-term outcomes, including mortality and cardiovascular morbidity were particularly important in decision making. There was ample evidence found on these outcomes.

#### 1.1.8.2 The quality of the evidence

The quality of the evidence ranged from very low to high. The main reasons for downgrading were due to inconsistency in the pooled estimates and serious or very serious imprecision. The committee noted that inconsistency between trials is likely due to the different targets for blood pressure in the trials, as this varied with most aiming to achieve a systolic blood pressure of 140 mm Hg or 130 mm Hg. Additionally, two trials included used mean arterial pressure (MAP), as opposed to systolic blood pressure, to measure arterial pressure and one trial (MDRD 1994) did not define blood pressure target in treatment arms.

The committee discussed the discrepancy in blood pressure targets and the measurements used from the perspective of pooling the studies for meta-analysis. Overall, given that it was primarily interested in the relative effects of a more intensive blood pressure control regimen compared to a less intensive one, the committee agreed that it was reasonable to combine the studies. The committee additionally noted that even though standard/low and intensive management regimens specified BP targets, in practice few people achieved the targets, especially in the intensive groups. The committee also considered a systolic blood pressure target range of 130 to 140 mm Hg, and the targets specified for MAP, to be consistent with clinical practice.

#### 1.1.8.3 Benefits and harms

In non-diabetic people, the committee noted that the majority of the evidence could not differentiate between BP targets or showed no meaningful difference between them. One outcome, 30 percent decline in eGFR or more per year, favoured standard blood pressure therapy in one large trial at low risk of bias. However, the committee took into account that the trial (SPRINT 2017) reported that the higher rate of eGFR decline in the intensive group was due to the acute (up to 6 months) effect of the intervention. Therefore, the outcome may not be generalisable to what occurs in long-term management. Another outcome which showed a meaningful difference was all-cause mortality in the same large trial at low risk of bias (SPRINT 2017), which reported lower mortality in the intensive blood pressure therapy group, however when this outcome was pooled with other trials in a meta-analysis, no meaningful difference was observed (although there was no serious imprecision).

The committee discussed the evidence in people with diabetes, which showed no meaningful differences between intensive and standard blood pressure therapy for cardiovascular outcomes and decline in eGFR. It noted that there is uncertainty in clinical practice around the particular need for intensive blood pressure therapies to reduce kidney disease progression and cardiovascular outcomes in people with diabetes and that this evidence did not help to resolve that. However, the committee did not think this was an area that needed to be prioritised for a research recommendation.

The committee discussed the evidence relating to populations with proteinuria, which was presented separately (see Appendix L). One study conducted in African American people, AASK 2002, reported lower risk of end-stage renal disease in participants who had 1 g/d or more proteinuria at baseline in the strict blood pressure therapy group compared to usual therapy. However, it noted that this was a relatively small (N=175) sample size and in an African-American population. Therefore, the committee was uncertain around the

generalisability of this evidence to the wider population of people with chronic kidney disease.

The committee discussed the 2014 recommendations and noted that the recommendation to keep blood pressure below 140 mmHg and the diastolic blood pressure below 90 mmHg is consistent with clinical practice and is consistent with the NICE guideline on managing hypertension. The committee noted that despite the limited evidence around blood pressure targets in CKD and proteinuria, it is important to maintain an adequate blood pressure within the normal range, and the committee agreed that is the 2014 recommendation of a systolic blood pressure below 130 mmHg and diastolic blood pressure below 80 mmHg was sensible. It agreed that none of the evidence it had seen warranted changing the recommendations. They also noted that intensive blood pressure targets only result in a marginal reduction in stroke and kidney failure, but put a large burden on patients (in terms of polypharmacy and associated risks and side effects (such as falls).

The committee discussed the finding from the ESCAPE 2004 trial. This trial was specifically in children and young people (under 18 years old), and reported that there was a significantly greater antihypertensive response in children with gross proteinuria than in children with mild or no proteinuria. The committee agreed that in clinical practice, the target for blood pressure in children and young people with CKD and proteinuria is to keep systolic blood pressure below 50th percentile for their corresponding height. In the absence of clearer evidence, the committee agreed to recommend this for children and young people based on committee consensus.

The committee looked at the evidence for other subgroups for which there were data, but agreed none of the data were useful for making recommendations for specific groups.

The committee discussed the adverse events that could be associated with BP management, particularly with regard to falls in dizziness in older people who became hypotensive from too tight a control of their BP. The committee noted that this concern was not borne out by the evidence, however it agreed to cross refer to the recommendations in the NICE hypertension guideline for people who were frail or had multiple health concerns.

#### 1.1.8.4 Cost effectiveness and resource use

The committee was not presented with any formal cost effectiveness evidence. The recommendations are unlikely to result in a substantial resource impact as the values are in line with current practice and previous recommendations. The new recommendation for children and young people is also unlikely to have a substantial resource impact as the monitoring is likely to happen in the usual monitoring appointment and any medications are very low cost.

### 1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 to 1.6.3.

### 1.1.10 References – included studies

#### 1.1.10.1 Effectiveness

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Wright, J.T., Williamson, J.D., Whelton, P.K. et al. (2015) A randomized trial of intensive versus standard blood-pressure control. New England Journal of Medicine 373(22): 2103-2116

Wright, Jackson T Jr, Agodoa, Lawrence, Contreras, Gabriel et al. (2002) Successful blood pressure control in the African American Study of Kidney Disease and Hypertension. Archives of internal medicine 162(14): 1636-43

Wuhl, Elke, Mehls, Otto, Schaefer, Franz et al. (2004) Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. Kidney international 66(2): 768-76

# Appendices

## Appendix A – Review protocols

**Review protocol for blood pressure control in chronic kidney disease**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | 1. CRD42019162567 |
| 1. | Review title | Blood pressure control in chronic kidney disease |
| 2. | Review question | In adults, children and young people with CKD, what are the optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality? |
| 3. | Objective | To determine the optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality in adults, children and young people with CKD. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR) |

| | | |
|---|---|---|
| | | • Embase<br>• MEDLINE<br><br>Searches will be restricted by:<br><br>• English language<br>• Human studies<br>• 2014 for adults<br><br>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | The Health Survey for England (2016) found that 13% of adults (16 years and over) had any CKD (stages 1 to 5). The prevalence of stages 3 to 5 was 5% for all adults, rising to 34% in people aged 75 and over. |
| 6. | Population | Inclusion:<br><br>Adults, children and young people with diagnosed chronic kidney disease GFR categories G1 to G5. |

| | | |
|---|---|---|
| 7. | Intervention/Exposure/Test | 'intense' or 'strict' blood pressure control (as defined by the author), including both drug and lifestyle interventions. |
| 8. | Comparator/Reference standard/Confounding factors | 'normal' management of BP (as defined by author), including any variation data, for example change from baseline. |
| 9. | Types of study to be included | • RCTs<br>• Systematic reviews of RCTs |
| 10. | Other exclusion criteria | • Abstracts and conference proceedings<br>• Theses<br>• Non-human studies |
| 11. | Context | NICE guideline CG182 chronic kidney disease in adults: assessment and management will be updated by this question. This guideline will be combined with guidelines CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia and NG 8 chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people. |

| | | |
|---|---|---|
| 12. | Primary outcomes (critical outcomes) | Over the follow up of the study:<br>• All-cause mortality<br>• Cardiovascular mortality and morbidity<br>• Heart failure<br>• Decline in eGFR or creatinine clearance<br>• Progression to ESRD or ESKD<br>• % of people reaching target BP<br>• Adverse events:<br>  ○ falls/fractures<br>  ○ postural hypotension<br>  ○ electrolyte disorders<br>Similar time-points will be grouped for analysis.<br>Results will be stratified by diabetic and non-diabetic populations. |
| 13. | Secondary outcomes (important outcomes) | The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making. |

| | | |
|---|---|---|
| 14. | Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the test and reference standard used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.<br><br>Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the Cochrane RoB v2.0 checklist as described in Developing NICE guidelines: the manual. |
| 16. | Strategy for data synthesis | Meta-analyses of primary and secondary outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).<br><br>Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after |

| | | |
|---|---|---|
| | | appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met:<br><br>Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis.<br><br>The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%.<br><br>Meta-analyses will be performed in Cochrane Review Manager V5.3 |
| 17. | Analysis of sub-groups | Where possible data will be stratified by<br><br>• Age<br><br>• Diabetes<br><br>• Ethnicity<br><br>• Stage of CKD<br><br>• Target BP<br><br>• Proteinuria/non-proteinuria |

| | | |
|---|---|---|
| 18. | Type and method of review | ☒ Intervention<br>☐ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) |
| 19. | Language | English |
| 20. | Country | England |
| 21. | Anticipated or actual start date | December 2019 |
| 22. | Anticipated completion date | December 2020 |

| | | | | |
|---|---|---|---|---|
| 23. | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | ☐ |
| | | Piloting of the study selection process | ☐ | ☐ |
| | | Formal screening of search results against eligibility criteria | ☐ | ☐ |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | **5a. Named contact**<br><br>Guideline Updates Team | | |

| | | |
|---|---|---|
| | | **5b Named contact e-mail**<br><br>GUTprospero@nice.org.uk<br><br>**5e Organisational affiliation of the review**<br><br>National Institute for Health and Care Excellence (NICE) |
| 25. | Review team members | From the Guideline Updates Team:<br><br>• Mr Chris Carmona<br>• Dr Yolanda Martinez<br>• Mr Gabriel Rogers<br>• Ms Hannah Nicholas<br>• Ms Lynda Ayiku<br>• Mr Rui Martins |

| | | |
|---|---|---|
| 26. | Funding sources/sponsor | This systematic review is being completed by the Guideline Updates Team which is part of NICE. |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website. |
| 29. | Other registration details | |
| 30. | Reference/URL for published protocol | |
| 31. | Dissemination plans | – NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: |

| | | |
|---|---|---|
| | | • notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 32. | Keywords | Chronic Kidney Disease, Blood pressure management, hypertension |
| 33. | Details of existing review of same topic by same authors | |
| 34. | Current review status | ☒ Ongoing<br>☐ Completed but not published<br>☐ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |
| 35.. | Additional information | |

| | | |
|---|---|---|
| 36. | Details of final publication | www.nice.org.uk |

# Appendix B – Methods

### Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

### Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately.

### Evidence of effectiveness of interventions

### Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

**Methods for combining intervention evidence**

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome on the same scale, a pooled mean difference was calculated. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

### Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as mean difference was available for a single study, an MID of the 0.5 of the comparison group arm was used. For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For dichotomous outcomes relating to mortality, the line of no effect (RR or HR = 1) was used. For dichotomous outcomes assessed using hazard data (hazard ratios), the line of no effect (HR = 1) was also used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

### GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 4.

**Table 4: Rationale for downgrading quality of evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. |
| Indirectness | Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| | Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies. |
| Inconsistency | Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the $I^2$ statistic.<br>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.<br>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.<br>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.<br>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes. |
| Imprecision | If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.<br>If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.<br>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios. |

**Interpreting effect**

Evidence statements for pairwise intervention data are classified in to one of four categories where default MIDs for risk ratios (0.8, 1.25) or MIDs for continuous outcomes (0.5 standard deviations of comparator group arm) was used:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is exceeds the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- Situations where the 95% confidence intervals crosses both MIDs, we state that the evidence could not differentiate between the comparators.

For outcomes where the MID is set as the line of no effect (in the case of mortality and hazard ratios), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

# Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 5.

**Table 5 Applicability criteria**

| Level | Explanation |
|---|---|
| Directly applicable | The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness |
| Partially applicable | The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness |
| Not applicable | The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration |

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 6.

**Table 6 Methodological criteria**

| Level | Explanation |
|---|---|
| Minor limitations | Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness |
| Potentially serious limitations | Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness |
| Very serious limitations | Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration |

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

# Appendix C – Literature search strategies

### Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run on the 15th of November 2019 and updated between the 10th and 16th of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

To retrieve evidence on adults that had been published since the search strategies were last run for the former guideline, the search was limited from 2011. No date restrictions were applied to the section of the search strategies on children and young people because this population had not been included in the former guideline.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

### Clinical searches

| Databases | Date searched | Version/files | No. retrieved |
|---|---|---|---|
| Cochrane Central Register of Controlled Trials (CENTRAL) | 15th Nov 2019 | Issue 11 of 12, November 2019 | 2035 |
| Cochrane Database of Systematic Reviews (CDSR) | 15th Nov 2019 | Issue 11 of 12, November 2019 | 77 |
| Database of Abstracts of Reviews of Effect (DARE)/HTA / NHS EED | 15th Nov 2019 | Up to 2015 | 130 |
| Embase (Ovid) | 15th Nov 2019 | Embase <1974 to 2019 November 14> | 2621 |

| | | | |
|---|---|---|---|
| MEDLINE (Ovid) | 15th Nov 2019 | Ovid MEDLINE(R) <1946 to November 14, 2019> | 1629 |
| MEDLINE In-Process (Ovid) | 15th Nov 2019 | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to November 14, 2019> | 218 |
| MEDLINE Epub Ahead of Print[a] | 15th Nov 2019 | Ovid MEDLINE(R) Epub Ahead of Print <November 14, 2019> | 39 |

The following search filters were applied in MEDLINE and Embase to identify RCTs and systematic reviews:

- RCT filters:
  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

    In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

    In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

| **Search strategies** |
|---|
| Database: Ovid MEDLINE(R) <1946 to November 14, 2019><br><br>Search Strategy:<br><br>----------<br><br>1 exp Renal Insufficiency, Chronic/ (110868) |

[a] Please search for both development and re-run searches

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (71049)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21124)

4 ckd*.tw. (22124)

5 ((kidney* or renal*) adj1 fail*).tw. (85702)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (34629)

7 (esrd* or eskd*).tw. (13916)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3428)

9 or/1-8 (209703)

10 exp Blood Pressure/ (285504)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (82087)

12 exp Hypertension/ (249165)

13 hypertensi*.tw. (375609)

14 or/10-13 (643661)

15 9 and 14 (30828)

16 randomized controlled trial.pt. (494259)

17 randomi?ed.mp. (766734)

18 placebo.mp. (189933)

19 or/16-18 (817436)

20 (MEDLINE or pubmed).tw. (149967)

21 systematic review.tw. (107976)

22 systematic review.pt. (116423)

23 meta-analysis.pt. (107741)

24 intervention$.ti. (116924)

25 or/20-24 (352469)

26 19 or 25 (1068201)

27 15 and 26 (3088)

28 limit 27 to english language (2916)

29 animals/ not humans/ (4609926)

30 28 not 29 (2832)

31 limit 30 to yr="2011 -Current" (1372)

32 exp Infant/ or Infant Health/ or Infant Welfare/ (1114337)

33 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (827677)

34 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1868833)

35 Minors/ (2544)

36 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2271661)

37 exp pediatrics/ (56493)

38 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (794431)

39 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1971780)

40 Puberty/ (13103)

41 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (405675)

42 Schools/ (36267)

43 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8683)

44 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (451693)

45 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (3762)

46 or/32-45 (5037663)

47 9 and 46 (45585)

48 14 and 26 and 47 (522)

49 limit 48 to english language (496)

50 animals/ not humans/ (4609926)

51 49 not 50 (488)

52 31 or 51 (1629)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to November 14, 2019>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9153)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1088)

4 ckd*.tw. (4303)

5 ((kidney* or renal*) adj1 fail*).tw. (6225)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4628)

7 (esrd* or eskd*).tw. (1939)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17928)

10 exp Blood Pressure/ (0)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (6917)

12 exp Hypertension/ (0)

13 hypertensi*.tw. (35024)

14 or/10-13 (38532)

15 9 and 14 (2747)

16 randomized controlled trial.pt. (276)

17 randomi?ed.mp. (68691)

18 placebo.mp. (16843)

19 or/16-18 (74715)

20 (MEDLINE or pubmed).tw. (32007)

21 systematic review.tw. (26420)

22 systematic review.pt. (490)

23 meta-analysis.pt. (39)

24 intervention$.ti. (19397)

25 or/20-24 (61730)

26 19 or 25 (122811)

27 15 and 26 (236)

28 limit 27 to english language (236)

29 animals/ not humans/ (0)

30 28 not 29 (236)

31 limit 30 to yr="2011 -Current" (217)

32 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

33 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (74533)

34 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

35 Minors/ (0)

36 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (295531)

37 exp pediatrics/ (0)

38 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (110573)

39 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

40 Puberty/ (0)

41 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (55291)

42 Schools/ (0)

43 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

44 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (64083)

45 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (563)

46 or/32-45 (428707)

47 9 and 46 (3288)

48 14 and 26 and 47 (44)

49 limit 48 to english language (44)

50 animals/ not humans/ (0)

51 49 not 50 (44)

52 31 or 51 (218)

Database: Ovid MEDLINE(R) Epub Ahead of Print <November 14, 2019>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1348)

3 ((kidney* or renal*) adj1 insufficien*).tw. (152)

4 ckd*.tw. (701)

5 ((kidney* or renal*) adj1 fail*).tw. (712)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (657)

7 (esrd* or eskd*).tw. (275)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2496)

10 exp Blood Pressure/ (0)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (1051)

12 exp Hypertension/ (0)

13 hypertensi*.tw. (4984)

14 or/10-13 (5509)

15 9 and 14 (374)

16 randomized controlled trial.pt. (1)

17 randomi?ed.mp. (12665)

18 placebo.mp. (2956)

19 or/16-18 (13661)

20 (MEDLINE or pubmed).tw. (6565)

21 systematic review.tw. (6250)

22 systematic review.pt. (23)

23 meta-analysis.pt. (13)

24 intervention$.ti. (3839)

25 or/20-24 (12843)

26 19 or 25 (23418)

27 15 and 26 (43)

28 limit 27 to english language (43)

29 animals/ not humans/ (0)

30 28 not 29 (43)

31 limit 30 to yr="2011 -Current" (38)

32 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

33 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (13907)

34 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

35 Minors/ (0)

36 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (47236)

37 exp pediatrics/ (0)

38 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (19460)

39 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

40 Puberty/ (0)

41 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (12126)

42 Schools/ (0)

43 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

44 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (11171)

45 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (96)

46 or/32-45 (69978)

47 9 and 46 (535)

48 14 and 26 and 47 (6)

49 limit 48 to english language (6)

50 animals/ not humans/ (0)

51 49 not 50 (6)

52 31 or 51 (39)

Database: Embase <1974 to 2019 November 14>

Search Strategy:

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1 exp kidney failure/ (343312)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (119892)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29758)

4 ckd*.tw. (47817)

5 ((kidney* or renal*) adj1 fail*).tw. (130502)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (56834)

7 (esrd* or eskd*).tw. (26599)

8 or/1-7 (434354)

9 exp *blood pressure/ (116722)

10 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or manag* or regulat*)).tw. (123913)

11 exp *hypertension/ (282642)

12 hypertensi*.tw. (616477)

13 or/9-12 (799393)

14 8 and 13 (58451)

15 (MEDLINE or pubmed).tw. (238630)

16 exp systematic review/ or systematic review.tw. (272033)

17 meta-analysis/ (176090)

18 intervention$.ti. (188662)

19 or/15-18 (611797)

20 random:.tw. (1477628)

21 placebo:.mp. (444304)

22 double-blind:.tw. (204516)

23 or/20-22 (1728434)

24 19 or 23 (2147867)

25 14 and 24 (6927)

26 limit 25 to yr="2011 -Current" (4227)

27 nonhuman/ not human/ (4505228)

28 26 not 27 (4125)

29 limit 28 to english language (4046)

30 limit 29 to (conference abstract or conference paper or "conference review") (1701)

31 29 not 30 (2345)

32 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3323114)

33 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1169060)

34 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3510914)

35 exp pediatrics/ (102363)

36 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1577568)

37 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (100452)

38 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (633468)

39 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (100138)

40 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (671915)

41 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (7048)

42 or/32-41 (6219192)

43 8 and 42 (85186)

44 13 and 24 and 43 (1051)

45 limit 44 to english language (1007)

46 nonhuman/ not human/ (4505228)

47 45 not 46 (979)

48 limit 47 to (conference abstract or conference paper or "conference review") (325)

49 47 not 48 (654)

50 31 or 49 (2621)

**Cochrane Library**

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees | 6131 |
| #2 | (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw | 9980 |
| #3 | (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw | 4820 |
| #4 | (ckd*):ti,ab,kw | 4643 |
| #5 | (((kidney* or renal*) near/1 fail*)):ti,ab,kw | 15994 |
| #6 | (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw | 4368 |
| #7 | ((esrd* or eskd*)):ti,ab,kw | 1986 |
| #8 | MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only | 83 |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 | 25167 |
| #10 | MeSH descriptor: [Blood Pressure] explode all trees | 26906 |

#11 ((blood pressure* or bp) near/3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)):ti,ab 50622

#12 MeSH descriptor: [Hypertension] explode all trees 16909

#13 (hypertensi*):ti,ab 52794

#14 #10 or #11 or #12 or #13 101212

#15 #9 and #14 4438

#16 "conference":pt or (clinicaltrials or trialsearch):so 440436

#17 #15 not 16 with Publication Year from 2011 to 2019, with Cochrane Library publication date Between Jan 2011 and Jan 2019, in Trials 1468

#18 #15 not #16 with Cochrane Library publication date Between Jan 2011 and Jan 2019 1253

#19 #17 or #18 1848

#20 MeSH descriptor: [Infant] explode all trees 15622

#21 MeSH descriptor: [Infant Health] this term only 40

#22 MeSH descriptor: [Infant Welfare] this term only 82

#23 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):ti,ab,kw 84610

#24 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):so 4967

#25 MeSH descriptor: [Child] explode all trees 1203

#26 MeSH descriptor: [Child Behavior] explode all trees 1962

#27 MeSH descriptor: [Child Health] this term only 87

#28 MeSH descriptor: [Child Welfare] this term only 323

#29 MeSH descriptor: [Minors] this term only 8

#30 ((child* or minor or minors or boy* or girl* or kid or kids or young*)):ti,ab,kw 254493

#31 ((child* or minor or minors or boy* or girl* or kid or kids or young*)):so 10193

#32 MeSH descriptor: [Pediatrics] explode all trees 648

#33 ((pediatric* or paediatric* or peadiatric*)):ti,ab,kw 32085

#34 ((pediatric* or paediatric* or peadiatric*)):so 31716

#35 MeSH descriptor: [Adolescent] this term only 101404

#36 MeSH descriptor: [Adolescent Behavior] this term only 1334

#37 MeSH descriptor: [Adolescent Health] this term only 22

#38 MeSH descriptor: [Puberty] this term only 298

#39 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)):ti,ab,kw 137043

#40 ((adolescen* or pubescen* or prepubescen* or pre-pubecen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or juvenil* or youth* or under*age*)):so 3706

#41 MeSH descriptor: [Schools] this term only 1815

#42 MeSH descriptor: [Child Day Care Centers] this term only 220

#43 MeSH descriptor: [Nurseries] this term only 9

#44 MeSH descriptor: [Schools, Nursery] this term only 37

#45 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):ti,ab,kw 93293

#46 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):so 1144

#47 (("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*")):ti,ab,kw 14230

#48 {or #20-#47} 402228

#49 #9 and #48 3960

#50 #14 and #49 781

#51 "conference":pt or (clinicaltrials or trialsearch):so 440436

#52 #50 not #51 493

#53 #19 or #52 2112 (2035 Central, 77 CDSR)

**CRD databases**

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 ((chronic* or progressi*) near1 (renal* or kidney*)) 489 Delete

3 ((kidney* or renal*) near1 insufficien*) 320 Delete

4 (ckd*) 93 Delete

5 ((kidney* or renal*) near1 fail*) 836 Delete

6 ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*)) 354 Delete

7 (esrd* or eskd*) 150 Delete

8 (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) 0 Delete

| | | | |
|---|---|---|---|
| 9 | (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) | 1407 | Delete |
| 10 | MeSH DESCRIPTOR Blood Pressure EXPLODE ALL TREES | 573 | Delete |
| 11 | ((blood pressure* or bp) near3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)) | 460 | Delete |
| 12 | MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES | 896 | Delete |
| 13 | (hypertensi*) | 2304 | Delete |
| 14 | (#10 or #11 or #12 or #13) | 2613 | Delete |
| 15 | #9 AND #14 | 251 | Delete |
| 16 | (#9 AND #14) IN DARE | 130 | Delete |

### Cost-effectiveness searches

| Databases | Date searched | Version/files | No. retrieved |
|---|---|---|---|
| MEDLINE (Ovid) | 15th Nov 2019 | Ovid MEDLINE(R) <1946 to November 14, 2019> | 1047 |
| MEDLINE in Process (Ovid) | 15th Nov 2019 | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations | 200 |
| MEDLINE epub (Ovid) | 15th Nov 2019 | Ovid MEDLINE(R) Epub Ahead of Print <November 14, 2019> | 19 |
| Embase (Ovid) | 15th Nov 2018 | Embase <1974 to 2019 Week 45> | 1848 |
| EconLit (Ovid) | 15th Nov 2019 | Econlit <1886 to October 24, 2019> | 5 |
| NHS Economic Evaluation Database (NHS EED) (legacy database) | 15th Nov 2019 | Up to 2015 | 106 |
| CRD HTA | 15th Nov 2019 | Up to 2018 | 15 |

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

  Several modifications have been made to these filters over the years that are standard NICE practice.

| **Search strategies** |
|---|
| Database: Ovid MEDLINE(R) <1946 to November 14, 2019> |
| Search Strategy: |
| --- |
| 1 exp Renal Insufficiency, Chronic/ (110868) |
| 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (71049) |
| 3 ((kidney* or renal*) adj1 insufficien*).tw. (21124) |
| 4 ckd*.tw. (22124) |
| 5 ((kidney* or renal*) adj1 fail*).tw. (85702) |
| 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (34629) |
| 7 (esrd* or eskd*).tw. (13916) |
| 8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3428) |
| 9 or/1-8 (209703) |
| 10 exp Blood Pressure/ (285504) |
| 11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (82087) |
| 12 exp Hypertension/ (249165) |
| 13 hypertensi*.tw. (375609) |
| 14 or/10-13 (643661) |
| 15 9 and 14 (30828) |
| 16 Economics/ (27101) |
| 17 exp "Costs and Cost Analysis"/ (230088) |
| 18 Economics, Dental/ (1908) |
| 19 exp Economics, Hospital/ (24009) |
| 20 exp Economics, Medical/ (14135) |

21 Economics, Nursing/ (3995)

22 Economics, Pharmaceutical/ (2897)

23 Budgets/ (11194)

24 exp Models, Economic/ (14500)

25 Markov Chains/ (13807)

26 Monte Carlo Method/ (27398)

27 Decision Trees/ (10780)

28 econom$.tw. (226875)

29 cba.tw. (9656)

30 cea.tw. (19964)

31 cua.tw. (960)

32 markov$.tw. (17190)

33 (monte adj carlo).tw. (28836)

34 (decision adj3 (tree$ or analys$)).tw. (12556)

35 (cost or costs or costing$ or costly or costed).tw. (439638)

36 (price$ or pricing$).tw. (32078)

37 budget$.tw. (22879)

38 expenditure$.tw. (47375)

39 (value adj3 (money or monetary)).tw. (1998)

40 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3409)

41 or/16-40 (889124)

42 "Quality of Life"/ (184297)

43 quality of life.tw. (217180)

44 "Value of Life"/ (5671)

45 Quality-Adjusted Life Years/ (11574)

46 quality adjusted life.tw. (10157)

47 (qaly$ or qald$ or qale$ or qtime$).tw. (8350)

48 disability adjusted life.tw. (2494)

49 daly$.tw. (2279)

50 Health Status Indicators/ (23093)

51 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21582)

52 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1282)

53 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4613)

54 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

55 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (373)

56 (euroqol or euro qol or eq5d or eq 5d).tw. (8196)

57 (qol or hql or hqol or hrqol).tw. (41343)

58 (hye or hyes).tw. (59)

59 health$ year$ equivalent$.tw. (38)

60 utilit$.tw. (163245)

61 (hui or hui1 or hui2 or hui3).tw. (1238)

62 disutili$.tw. (363)

63 rosser.tw. (90)

64 quality of wellbeing.tw. (13)

65 quality of well-being.tw. (370)

66 qwb.tw. (187)

67 willingness to pay.tw. (4129)

68 standard gamble$.tw. (770)

69 time trade off.tw. (1001)

70 time tradeoff.tw. (225)

71 tto.tw. (868)

72 or/42-71 (469156)

73 41 or 72 (1293213)

74 15 and 73 (2062)

75 limit 74 to yr="2011 -Current" (893)

76 limit 75 to english language (823)

77 animals/ not humans/ (4609926)

78 76 not 77 (810)

79 exp Infant/ or Infant Health/ or Infant Welfare/ (1114337)

80 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (827677)

81 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1868833)

82 Minors/ (2544)

83 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2271661)

84 exp pediatrics/ (56493)

85 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (794431)

86 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1971780)

87 Puberty/ (13103)

88 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (405675)

89 Schools/ (36267)

90 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8683)

91 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (451693)

92 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (3762)

93 or/79-92 (5037663)

94 9 and 93 (45585)

95 14 and 73 and 94 (518)

96 limit 95 to english language (467)

97 animals/ not humans/ (4609926)

98 96 not 97 (466)

99 78 or 98 (1047)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to November 14, 2019>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9153)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1088)

4 ckd*.tw. (4303)

5 ((kidney* or renal*) adj1 fail*).tw. (6225)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4628)

7 (esrd* or eskd*).tw. (1939)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17928)

10 exp Blood Pressure/ (0)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (6917)

12 exp Hypertension/ (0)

13 hypertensi*.tw. (35024)

14 or/10-13 (38532)

15 9 and 14 (2747)

16 Economics/ (0)

17 exp "Costs and Cost Analysis"/ (0)

18 Economics, Dental/ (0)

19 exp Economics, Hospital/ (0)

20 exp Economics, Medical/ (0)

21 Economics, Nursing/ (0)

22 Economics, Pharmaceutical/ (0)

23 Budgets/ (0)

24 exp Models, Economic/ (0)

25 Markov Chains/ (0)

26 Monte Carlo Method/ (0)

27 Decision Trees/ (0)

28 econom$.tw. (41689)

29 cba.tw. (405)

30 cea.tw. (1792)

31 cua.tw. (196)

32 markov$.tw. (5311)

33 (monte adj carlo).tw. (16328)

34 (decision adj3 (tree$ or analys$)).tw. (2204)

35 (cost or costs or costing$ or costly or costed).tw. (89554)

36 (price$ or pricing$).tw. (5442)

37 budget$.tw. (4697)

38 expenditure$.tw. (6103)

39 (value adj3 (money or monetary)).tw. (346)

40 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (516)

41 or/16-40 (155518)

42 "Quality of Life"/ (0)

43 quality of life.tw. (36079)

44 "Value of Life"/ (0)

45 Quality-Adjusted Life Years/ (0)

46 quality adjusted life.tw. (1520)

47 (qaly$ or qald$ or qale$ or qtime$).tw. (1281)

48 disability adjusted life.tw. (469)

49 daly$.tw. (433)

50 Health Status Indicators/ (0)

51 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2547)

52 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (719)

53 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (701)

54 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)

55 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)

56 (euroqol or euro qol or eq5d or eq 5d).tw. (1566)

57 (qol or hql or hqol or hrqol).tw. (6903)

58 (hye or hyes).tw. (6)

59 health$ year$ equivalent$.tw. (2)

60 utilit$.tw. (29077)

61 (hui or hui1 or hui2 or hui3).tw. (171)

62 disutili$.tw. (67)

63 rosser.tw. (5)

64 quality of wellbeing.tw. (6)

65 quality of well-being.tw. (32)

66 qwb.tw. (11)

67 willingness to pay.tw. (860)

68 standard gamble$.tw. (56)

69 time trade off.tw. (119)

70 time tradeoff.tw. (17)

71 tto.tw. (117)

72 or/42-71 (67447)

73 41 or 72 (214178)

74 15 and 73 (237)

75 limit 74 to yr="2011 -Current" (203)

76 limit 75 to english language (200)

77 animals/ not humans/ (0)

78 76 not 77 (200)

79 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

80 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (74533)

81 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

82 Minors/ (0)

83 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (295531)

84 exp pediatrics/ (0)

85 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (110573)

86 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

87 Puberty/ (0)

88 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (55291)

89 Schools/ (0)

90 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

91 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (64083)

92 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (563)

93 or/79-92 (428707)

94 9 and 93 (3288)

95 14 and 73 and 94 (49)

96 limit 95 to english language (49)

97 animals/ not humans/ (0)

98 96 not 97 (49)

99 78 or 98 (200)

Database: Ovid MEDLINE(R) Epub Ahead of Print <November 14, 2019>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1348)

3 ((kidney* or renal*) adj1 insufficien*).tw. (152)

4 ckd*.tw. (701)

5 ((kidney* or renal*) adj1 fail*).tw. (712)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (657)

7 (esrd* or eskd*).tw. (275)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2496)

10 exp Blood Pressure/ (0)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (1051)

12 exp Hypertension/ (0)

13 hypertensi*.tw. (4984)

14 or/10-13 (5509)

15 9 and 14 (374)

16 Economics/ (0)

17 exp "Costs and Cost Analysis"/ (0)

18 Economics, Dental/ (0)

19 exp Economics, Hospital/ (0)

20 exp Economics, Medical/ (0)

21 Economics, Nursing/ (0)

22 Economics, Pharmaceutical/ (0)

23 Budgets/ (0)

24 exp Models, Economic/ (0)

25 Markov Chains/ (0)

26 Monte Carlo Method/ (0)

27 Decision Trees/ (0)

28 econom$.tw. (5756)

29 cba.tw. (61)

30 cea.tw. (301)

31 cua.tw. (19)

32 markov$.tw. (693)

33 (monte adj carlo).tw. (1148)

34 (decision adj3 (tree$ or analys$)).tw. (379)

35 (cost or costs or costing$ or costly or costed).tw. (11982)

36 (price$ or pricing$).tw. (873)

37 budget$.tw. (525)

38 expenditure$.tw. (1138)

39 (value adj3 (money or monetary)).tw. (62)

40 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (46)

41 or/16-40 (19631)

42 "Quality of Life"/ (0)

43 quality of life.tw. (6597)

44 "Value of Life"/ (0)

45 Quality-Adjusted Life Years/ (0)

46 quality adjusted life.tw. (396)

47 (qaly$ or qald$ or qale$ or qtime$).tw. (340)

48 disability adjusted life.tw. (89)

49 daly$.tw. (74)

50 Health Status Indicators/ (0)

51 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (444)

52 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (45)

53 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (155)

54 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (1)

55 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)

56 (euroqol or euro qol or eq5d or eq 5d).tw. (345)

57 (qol or hql or hqol or hrqol).tw. (1307)

58 (hye or hyes).tw. (2)

59 health$ year$ equivalent$.tw. (0)

60 utilit$.tw. (4643)

61 (hui or hui1 or hui2 or hui3).tw. (18)

62 disutili$.tw. (15)

63 rosser.tw. (0)

64 quality of wellbeing.tw. (1)

65 quality of well-being.tw. (5)

66 qwb.tw. (3)

67 willingness to pay.tw. (156)

68 standard gamble$.tw. (8)

69 time trade off.tw. (19)

70 time tradeoff.tw. (4)

71 tto.tw. (18)

72 or/42-71 (11489)

73 41 or 72 (29389)

74 15 and 73 (23)

75 limit 74 to yr="2011 -Current" (19)

76 limit 75 to english language (19)

77 animals/ not humans/ (0)

78 76 not 77 (19)

79 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

80 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (13907)

81 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

82 Minors/ (0)

83 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (47236)

84 exp pediatrics/ (0)

85 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (19460)

86 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

87 Puberty/ (0)

88 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (12126)

89 Schools/ (0)

90 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

91 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (11171)

92 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (96)

93 or/79-92 (69978)

94 9 and 93 (535)

95 14 and 73 and 94 (6)

96 limit 95 to english language (6)

97 animals/ not humans/ (0)

98 96 not 97 (6)

99 78 or 98 (19)

Database: Embase <1974 to 2019 Week 45>

Search Strategy:

---

1 exp kidney failure/ (342577)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (119580)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29732)

4 ckd*.tw. (47652)

5 ((kidney* or renal*) adj1 fail*).tw. (130313)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (56712)

7 (esrd* or eskd*).tw. (26548)

8 or/1-7 (433583)

9 exp *blood pressure/ (116573)

10 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or manag* or regulat*)).tw. (123749)

11 exp *hypertension/ (282218)

12 hypertensi*.tw. (615366)

13 or/9-12 (797975)

14 8 and 13 (58332)

15 exp Health Economics/ (818210)

16 exp "Health Care Cost"/ (282535)

17 exp Pharmacoeconomics/ (197433)

18 Monte Carlo Method/ (37645)

19 Decision Tree/ (11840)

20 econom$.tw. (346759)

21 cba.tw. (12495)

22 cea.tw. (33372)

23 cua.tw. (1421)

24 markov$.tw. (28316)

25 (monte adj carlo).tw. (45056)

26 (decision adj3 (tree$ or analys$)).tw. (21634)

27 (cost or costs or costing$ or costly or costed).tw. (726569)

28 (price$ or pricing$).tw. (54186)

29 budget$.tw. (36670)

30 expenditure$.tw. (71450)

31 (value adj3 (money or monetary)).tw. (3281)

32 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8384)

33 or/15-32 (1673376)

34 "Quality of Life"/ (445314)

35 Quality Adjusted Life Year/ (24959)

36 Quality of Life Index/ (2682)

37 Short Form 36/ (27238)

38 Health Status/ (122969)

39 quality of life.tw. (413195)

40 quality adjusted life.tw. (18409)

41 (qaly$ or qald$ or qale$ or qtime$).tw. (18799)

42 disability adjusted life.tw. (3738)

43 daly$.tw. (3690)

44 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (39899)

45 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2259)

46 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8957)

47 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (56)

48 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (440)

49 (euroqol or euro qol or eq5d or eq 5d).tw. (19043)

50 (qol or hql or hqol or hrqol).tw. (90991)

51 (hye or hyes).tw. (128)

52 health$ year$ equivalent$.tw. (41)

53 utilit$.tw. (273510)

54 (hui or hui1 or hui2 or hui3).tw. (2151)

55 disutili$.tw. (864)

56 rosser.tw. (118)

57 quality of wellbeing.tw. (40)

58 quality of well-being.tw. (467)

59 qwb.tw. (239)

60 willingness to pay.tw. (8048)

61 standard gamble$.tw. (1080)

62 time trade off.tw. (1649)

63 time tradeoff.tw. (286)

64 tto.tw. (1585)

65 or/34-64 (936839)

66 33 or 65 (2461606)

67 14 and 66 (5301)

68 limit 67 to english language (4987)

69 limit 68 to (conference abstract or conference paper or "conference review") (2086)

70 68 not 69 (2901)

71 nonhuman/ not human/ (4496389)

72 70 not 71 (2883)

73 limit 72 to yr="2011 -Current" (1590)

74 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3318344)

75 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1167043)

76 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3504069)

77 exp pediatrics/ (102143)

78 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1574185)

79 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (100237)

80 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (632040)

81 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (99977)

82 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (670661)

83 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (7027)

84 or/74-83 (6208994)

85 8 and 84 (85055)

86 13 and 66 and 85 (1188)

87 limit 86 to english language (1128)

88 limit 87 to (conference abstract or conference paper or "conference review") (502)

89 87 not 88 (626)

90 nonhuman/ not human/ (4496389)

91 89 not 90 (624)

92 73 or 91 (1848)

Database: Econlit <1886 to October 24, 2019>

Search Strategy:

---

1 [exp Renal Insufficiency, Chronic/] (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (20)

3 ((kidney* or renal*) adj1 insufficien*).tw. (3)

4 ckd*.tw. (4)

5 ((kidney* or renal*) adj1 fail*).tw. (32)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (53)

7 (esrd* or eskd*).tw. (30)

8 ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)

9 or/1-8 (97)

10 [exp Blood Pressure/] (0)

11 ((blood pressure* or bp) adj3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)).tw. (34)

12 [exp Hypertension/] (0)

13 hypertensi*.tw. (258)

14 or/10-13 (283)

15 9 and 14 (5)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 ((chronic* or progressi*) near1 (renal* or kidney*)) 489 Delete

3 ((kidney* or renal*) near1 insufficien*) 320 Delete

4 (ckd*) 93 Delete

5 ((kidney* or renal*) near1 fail*) 836 Delete

6 ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*)) 354 Delete

7 (esrd* or eskd*) 150 Delete

8 (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) 0 Delete

9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) 1407 Delete

10 MeSH DESCRIPTOR Blood Pressure EXPLODE ALL TREES 573 Delete

11 ((blood pressure* or bp) near3 (lower* or control* or decreas* or reduc* or optim* or target* or goal* or rang* or manag* or regulat*)) 460 Delete

12 MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES 896 Delete

13 (hypertensi*) 2304 Delete

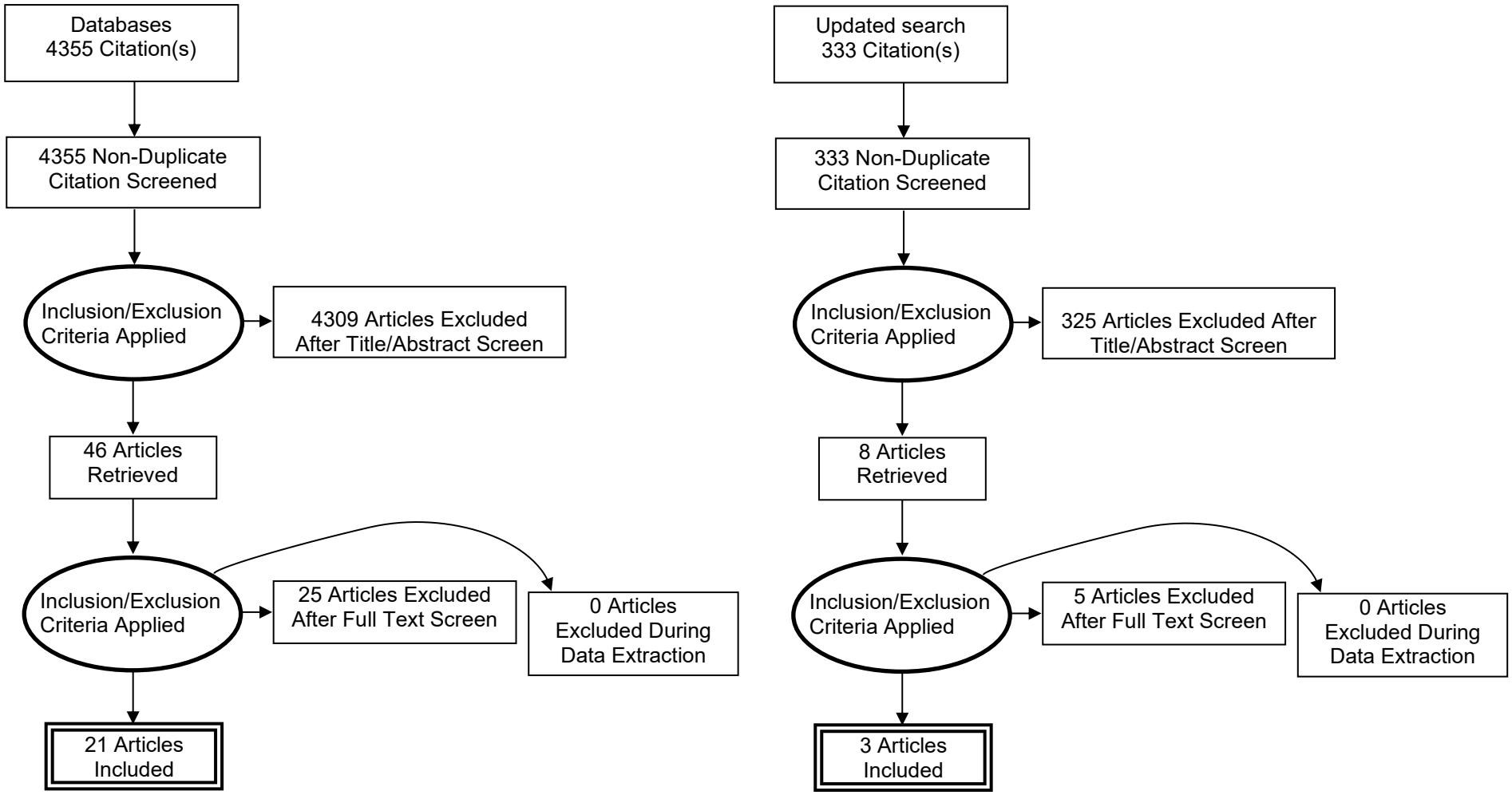
14 (#10 or #11 or #12 or #13) 2613 Delete

15 #9 AND #14 251 Delete

16 (#9 AND #14) IN HTA 15 Delete

17 (#9 AND #14) IN NHSEED 106 Delete

# Appendix D – Effectiveness evidence study selection



# Appendix E – Effectiveness evidence tables

## Agarwal, 2019

| | |
|---|---|
| **Bibliographic Reference** | Agarwal, A.; Cheung, A.K.; Ma, J.; Cho, M.; Li, M.; Effect of Baseline Kidney Function on the Risk of Recurrent Stroke and on Effects of Intensive Blood Pressure Control in Patients With Previous Lacunar Stroke: A Post Hoc Analysis of the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes); Journal of the American Heart Association; 2019; vol. 8 (no. 16); e013098 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | North America, Latin America, and Spain. |
| **Study setting** | 81 centres |
| **Duration of follow-up** | intended follow-up was to be on average for around 4 years. |
| **Sources of funding** | "The SPS3 (Secondary Prevention of Small Subcortical Strokes)<br>Trial was conducted by SPS3 Trial investigators and supported by a grant (U01NS038529) from the National Institutes of Health–National Institute of Neurological Disorders and Stroke<br>(NIH-NINDS)." |
| **Inclusion criteria** | eGFR<br>Participants were required to have a GFR of over 40. This post-hoc analysis looks at participants with <60 eGFR (and separately at those with >60 eGFR however these data were not extracted for this review). Therefore participants in the low eGFR subgroup analysis had an eGFR of 40-59.<br><br>symptomatic lacunar stroke |

| | |
|---|---|
| | Randomized within 6 months of a symptomatic S3 with MRI confirmation, with each of the following: clinical lacunar stroke syndrome; absence of signs or symptoms of cortical dysfunction; no ipsilateral cervical carotid stenosis (≥ 50%) if the qualifying event is hemispheric, and; no major-risk cardioembolic source requiring anticoagulation or other specific therapy (minor-risk cardioembolic sources are allowed if anticoagulation is not prescribed). Lacunar TIAs require positive MRI diffusion imaging to be eligible (see paper for more detail on eligibility criteria for lacunar TIAs) |
| **Sample size** | 474 |
| **Condition specific characteristics** | eGFR, mean (SD), ml/min per 1.73 m2<br>although supposedly excluded from the trial, 41 participants had an eGFR <40 ml/min/1.73m2 |
| **Interventions** | Intensive versus standard blood pressure control<br>Participants were randomized to either 'intensive' (<130 mmHg) or 'usual' (130–149 mmHg) systolic blood pressure targets. ll participants received enteric-coated aspirin 325 mg daily and are randomly assigned (double-blind) to take clopidogrel 75 mg daily or the matching placebo. "Participant blood pressure is managed locally at each clinical centre by a physician with expertise in blood pressure management. A recommended algorithm, based on JNC-VII guidelines (74), is provided to all sites to assist with blood pressure management (http:// www.sps3.org). The algorithm advocates titration of dose, as well as the addition of agents, using a step-wise approach, monitoring carefully for specific side effects of agents or due to lowering of blood pressure. Patients are seen at least monthly for adjustment of antihypertensive medications to achieve the assigned target blood pressure. Once the systolic blood pressure is in the assigned target range at two consecutive visits, the participant continues with quarterly follow-ups. To maximise adherence, blood pressure medications are provided free of charge to participants as deemed appropriate by the site hypertension expert. One or two drugs from each of the major classes of antihypertensive medications and additional medications on a case-by-case basis are available." |
| **Outcome measures** | All-cause mortality<br><br>Cardiovascular outcomes<br>Acute MI or stroke |

**Study arms**

| **Strict blood pressure control (SBP <130 mmHg) (N = 247)** | |
|---|---|
| % Female | 50.6% |
| Mean age (SD) | 69.3 (11.4) |

| | |
|---|---|
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>51.1 (6.9)<br>BP, mean (SD), mm Hg<br>SBP: 147.3 (21.0); DBP: 76.9 (11.1)<br>Diabetes mellitus (%)<br>37.7%<br>medications used<br>No. of antihypertensive drugs, mean (SD): 2.0 (1.2)<br>Race<br>% Black: 13.4%; % Hispanic: 29.6%; % non-Hispanic white: 54.3%<br>Hypertension (%)<br>88.3%<br>Total cholesterol, mean (SD), mg/dL<br>175.1 (52.4)<br>Smoking (%)<br>Current: 10.9%; Past: 45.7%; Never: 43.4%<br>Statin use (%)<br>70.9% |
| **Standard blood pressure control (SBP 130 - 149 mmHg) (N = 227)** | |
| % Female | 40.1% |
| Mean age (SD) | 69.4 (10.9) |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>50.9 (7.1)<br>BP, mean (SD), mm Hg<br>SBP: 146.8 (21.0); DBP: 77.9 (11.6)<br>Diabetes mellitus (%)<br>32.6%<br>medications used<br>No. of antihypertensive drugs, mean (SD): 1.9 (1.2)<br>Race |

| | |
|---|---|
| | Black: 15.9%; Hispanic: 24.7%; non-Hispanic white: 56.4%<br>Hypertension (%)<br>86.3%<br>Total cholesterol, mean (SD), mg/dL<br>174.0 (56.8)<br>Smoking (%)<br>Current: 14.1%; Past: 44.1%; Never: 41.9%<br>Statin use (%)<br>67.0% |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?*

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Cheung, 2017

| | |
|---|---|
| **Bibliographic Reference** | Cheung, Alfred K; Rahman, Mahboob; Reboussin, David M; Craven, Timothy E; Greene, Tom; Kimmel, Paul L; Cushman, William C; Hawfield, Amret T; Johnson, Karen C; Lewis, Cora E; Oparil, Suzanne; Rocco, Michael V; Sink, Kaycee M; Whelton, Paul K; Wright, Jackson T Jr; Basile, Jan; Beddhu, Srinivasan; Bhatt, Udayan; Chang, Tara I; Chertow, Glenn M; Chonchol, Michel; Freedman, Barry I; Haley, William; Ix, Joachim H; Katz, Lois A; Killeen, Anthony A; Papademetriou, Vasilios; Ricardo, Ana C; Servilla, Karen; Wall, Barry; Wolfgram, Dawn; Yee, Jerry; SPRINT Research, Group; Effects of Intensive BP Control in CKD.; Journal of the American Society of Nephrology : JASN; 2017; vol. 28 (no. 9); 2812-2823 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the SPRINT trial (Wright 2015), using only data for people with CKD |
| **Study location** | USA |
| **Study setting** | 102 clinical sites |
| **Study dates** | November 2010 and March 2013 |
| **Duration of follow-up** | The median follow-up on August 20, 2015, was 3.26 years of the planned average of 5 years. |
| **Sources of funding** | sponsored by the National Heart, Lung and Blood Institute; the National Institute of Diabetes and Digestive and Kidney Diseases; the National Institute of Neurologic Disorders and Stroke; and the National Institute on Aging |

| | |
|---|---|
| **Inclusion criteria** | age<br>at least 50 years of age<br><br>blood pressure<br>an SBP of 130–180mmHg<br><br>Increased risk for CVD events<br>CKD, defined as an eGFR of 20–59ml/min per 1.73m2, per se was considered a sufficient criterion for increased CVD risk and specifically targeted for recruitment<br><br>CKD |
| **Exclusion criteria** | Diabetes mellitus<br><br>Proteinuria<br>>1 g/d<br><br>polycystic kidney disease<br><br>cardiovascular criteria<br>prior stroke, symptomatic heart failure, and a left ventricular ejection fraction < 35% |
| **Sample size** | 2646 |
| **% Female** | 40% |
| **Mean age (SD)** | 71.9 (SD 9.3) years. 43.9% were 75 years or older. |
| **Interventions** | Intensive versus standard blood pressure control<br>Antihypertensive regimens were adjusted by site investigators to achieve and maintain SBP according to their study group assignment using published algorithms. Use of medications indicated for specific conditions (for example, renin-angiotensin blockers for proteinuric CKD) was encouraged. Healthy lifestyles for BP control and CVD protection (e.g., physical activity) were recommended but not specifically monitored. |
| **Outcome measures** | All-cause mortality<br>subgroup analysis available for age (over and under 75 years), sex, race (black versus non-black), kidney function (eGFR above or below the median) and Albuminuria (ACR above or below the median) |

| | |
|---|---|
| | adverse events<br>injurious fall and hypotension (reported separately)<br><br>acute renal failure<br><br>Cardiovascular outcomes<br>nonfatal myocardial infarction, non-myocardial infarction acute coronary syndrome, nonfatal acute decompensated heart failure, nonfatal stroke, and death from CVD causes.<br><br>eGFR decline<br>composite of a ≥50% decrease in eGFR or the development of end-stage renal disease |

**Study arms**

| | |
|---|---|
| **Intensive control (<120mmHg) (N = 1330)** | |
| % Female | 40.4% |
| Mean age (SD) | 72.0 (SD 9.0) years. 43.9% were 75 years or older. |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>47.9 (9.5)<br>BP, mean (SD), mm Hg<br>SBP: 139.1 (16.1); DBP 75.1 (12.2) |
| standard control (<140 mmHg) (N = 1316) | |
| % Female | 39.6% |
| Mean age (SD) | 71.9 (SD 9.5) years. 43.8% were 75 years or older. |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>47.9 (9.5)<br>BP, mean (SD), mm Hg<br>SDP: 139.2 (16.0); DBP 74.8 (12.2) |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?*

Yes

*4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?*

No

*(Objective outcomes)*

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*(Open-label but not at high risk of bias as all outcomes were objective. )*

*Overall Directness*

Directly applicable

## Hayashi, 2010

| | |
|---|---|
| **Bibliographic Reference** | Hayashi, K; Saruta, T; Goto, Y; Ishii, M; Impact of renal function on cardiovascular events in elderly hypertensive patients treated with efonidipine; Hypertension research; 2010; vol. 33 (no. 11); 1211-1220 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the JATOS trial (JATOS study group, 2005), providing a subgroup analysis for people with an eGFR of under 60 ml/min/1.73m2 |
| **Study location** | Japan |
| **Study dates** | Patients were enrolled from April 2001 to December 2002, and the trial period ended in December 2004 |
| **Duration of follow-up** | 2 years |
| **Sources of funding** | sponsored by Shionogi, Osaka, Japan. |
| **Inclusion criteria** | age<br>aged 65–85 years<br><br>blood pressure<br>manifested sustained hypertension with systolic BP over 160mmHg |
| **Exclusion criteria** | Diabetes mellitus<br>poorly controlled diabetes mellitus (fasting blood glucose 200mg dl-1 or more or HbA1c 8.0% or more)<br><br>cardiovascular criteria |

| | |
|---|---|
| | recent history of stroke, angina pectoris requiring hospitalization, congestive heart failure (New York Heart Association X class II), persistent arrhythmia (for example, atrial fibrillation), dissecting aneurysm<br><br>severe hypertension (diastolic BP 120mmHg or more)<br>or secondary hypertension<br><br>CKD<br>CKD with serum creatinine level 1.5mg dl-1 or more<br><br>Other<br>malignant disease or collagen disease |
| **Sample size** | 2,499 |
| **Interventions** | Intensive versus standard blood pressure control<br>"Participants were randomized to strict or mild blood pressure control (strict-treatment group: <140mmHg, and mild-treatment group; 140 to <160mmHg)Antihypertensive therapy with efonidipine (20–60mg per day), a long-acting Ca channel blocker with renal afferent and efferent arteriolar dilator action,16–20 was given to all patients, and if the target systolic BP was not achieved, additional antihypertensive agents, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics and b-blockers, were administered." |
| **Outcome measures** | eGFR decline<br>ESRD or doubling of serum creatinine levels |

**Study arms**

| | |
|---|---|
| **strict target (systolic blood pressure <120 mmHg) (N = 1230)** | |
| % Female | 62.7% |
| Mean age (SD) | 74.1 (5.5) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>48.8 (6.8)<br>BP, mean (SD), mm Hg<br>SBP: 171.7(9.5); DBP: 89.1(9.5)<br>Diabetes mellitus (%)<br>11.6% |
| **mild target (systolic blood pressure 140 to <160 mmHg) (N = 1269)** | |
| % Female | 65.3% |
| Mean age (SD) | 74.2 (5.3) |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>48.8 (6.5)<br>BP, mean (SD), mm Hg<br>SBP: 171.8 (9.8); DBP: 88.7 (9.7)<br>Diabetes mellitus (%)<br>12.2% |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

No information

*(Unclear how randomisation was undertaken. )*

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No

*(Open-label study. )*

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

High

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

Yes

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?*

Yes

*4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?*

No

*(Objective outcomes )*

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*(Objective outcomes included from open-label trial. )*

*Overall Directness*

Directly applicable

## Klahr, 1994

| | |
|---|---|
| **Bibliographic Reference** | Klahr S; Levey AS; Beck GJ; Caggiula AW; Hunsicker L; Kusek JW; Striker G; The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group.; The New England journal of medicine; 1994; vol. 330 (no. 13) |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | USA |
| **Duration of follow-up** | Participants underwent a 3 months baseline period before randomization. During this time blood pressure, creatinine clearance, and urinary protein excretion were measured initially and then every month. Following randomization protein intake was assessed monthly on the basis of 24-hour urinary excretion of urea nitrogen. The intake of protein, calories, and other nutrients was assessed every two months on the basis of three-day dietary records. Blood pressure was measured monthly, and when necessary, adjustments in therapy were made monthly or more often. The glomerular filtration rate was measured at two months, at four months, and every four months thereafter on the basis of the renal clearance of iothalamate. Anthropometric measurements were obtained every four months. Mean post-randomization follow-up was 2.2 years. |
| **Inclusion criteria** | age<br>18 to 70 years old<br><br>blood pressure<br>Mean arterial pressure of 125 mmHg or less<br><br>Serum creatinine<br>1.2 to 7.0 mg/dl in women and 1.4 to 7.0 mg/dl in men; or a creatinine clearance of <70ml/min/1.73m2<br><br>Protein intake<br>≥ 0.9 g per kilogram of body weight per day<br><br>GFR<br>25 to 55 ml per minute per 1.73 m2 |

| | |
|---|---|
| **Exclusion criteria** | Diabetes mellitus<br>If requiring insulin therapy<br><br>Other<br>urinary protein excretion exceeding 10 g per day, a history of renal transplantation or chronic medical conditions, or doubts about compliance<br><br>pregnancy<br><br>Body weight<br>" under 80 percent or over 160 percent of standard body weight" |
| **Sample size** | 585 |
| **Loss to follow-up** | 11 participants were lost to follow-up |
| **% Female** | 40% |
| **Mean age (SD)** | 52 years |
| **Condition specific characteristics** | BP, mean (SD), mm Hg<br>SBP: 131 (18); DBP: 81 (10); MAP 98 (11)<br><br>GFR, mean (SD), ml/min per 1.73 m2<br>38.6 (8.9)<br><br>Creatinine clearance, mean (SD), ml/min/1.73m2<br>50.4 (13.1) |

**Study arms**

| |
|---|
| **Standard MAP (N = 285)** |

MAP: 107 mmHg or less in participants aged 18 to 60 year, or 113 mmHg or less for participants aged 61 years or older. 140 participants were randomized to low protein diet: 0.58 grams of protein (with at least 0.35g of protein high in essential amino acids) and 5-10mg of phosphorus per kg of standard body weight. 145 participants were randomized to a standard protein diet: 1.3g of protein and 16-20mg of phosphorus per kg of standard body weight.

| | |
|---|---|
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 132 (17); DBP: 80 (10); MAP 97 (10)<br>GFR, mean (SD), ml/min per 1.73 m2<br>37.6 (9.0)<br>Creatinine clearance, mean (SD), ml/min/1.73m2<br>49.2 (12.6)<br>Protein, mean (SD), g/kg/day<br>1.12 (0.18)<br>total calories, mean (SD), kcal, kg, day<br>27.6 (7.0) |

**Low MAP (N = 300)**

MAP: 92 mmHg or less for participants aged 18 to 60 years, or 98 mmHg or less for participants aged 61 years or older. 151 participants were randomized to a low protein diet: 0.58 grams of protein (with at least 35g of protein high in essential amino acids) and 5-10mg of phosphorus per kg of standard body weight. 149 participants were randomized to a standard protein diet: 1.3g of protein and 16-20mg of phosphorus per kg of standard body weight.

| | |
|---|---|
| Study setting | Multiple centres |
| Sources of funding | Supported by the National Institute of Diabetes and Digestive and Kidney Diseases and the Health Care Financing Administration |
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 131 (19); DBP: 81 (10); MAP 98 (11) |

| | |
|---|---|
| | GFR, mean (SD), ml/min per 1.73 m2<br>38.2 (8.6)<br>Creatinine clearance, mean (SD), ml/min/1.73m2<br>49.2 (11.6)<br>Protein, mean (SD), g/kg/day<br>1.12 (0.18)<br>total calories, mean (SD), kcal, kg, day<br>26.8 (6.8) |
| Interventions | Intensive versus standard blood pressure control<br>Participants were randomized to protein diet (low or usual levels of daily protein) and a mean arterial blood pressure target (low or standard) |
| Outcome measures | acute renal failure<br>end-stage renal disease<br>eGFR decline<br>"The rate of change in the glomerular filtration rate (the slope) was the primary outcome measure. Slopes were calculated on the basis of the final base-line glomerular filtration rate and all follow-up rates without adjustment for the body-surface area." |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No information

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*(No information regarding randomisation process or allocation concealment. )*

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

*(No concern regarding lack of information about concealment as all outcomes are objective. )*

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

No information

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Pajewski, 2020

| | |
|---|---|
| **Bibliographic Reference** | Pajewski, N.M.; Berlowitz, D.R.; Bress, A.P.; Callahan, K.E.; Cheung, A.K.; Fine, L.J.; Gaussoin, S.A.; Johnson, K.C.; King, J.; Kitzman, D.W.; Kostis, J.B.; Lerner, A.J.; Lewis, C.E.; Oparil, S.; Rahman, M.; Reboussin, D.M.; Rocco, M.V.; Snyder, J.K.; Still, C.; Supiano, M.A.; Wadley, V.G.; Whelton, P.K.; Wright, J.T.; Williamson, J.D.; Intensive vs Standard Blood Pressure Control in Adults 80 Years or Older: A Secondary Analysis of the Systolic Blood Pressure Intervention Trial; Journal of the American Geriatrics Society; 2020; vol. 68 (no. 3); 496-504 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the SPRINT trial (Wright 2015), adults aged 80 years and older |
| **Study location** | US |
| **Study setting** | 102 clinical sites |
| **Study dates** | November 2010 and July 2016 |
| **Duration of follow-up** | Median 3.7 years |
| **Sources of funding** | Funded by the National Institutes of Health (including the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke); the Department of Veterans Affairs; azilsartan and chlorthalidone (combined with azilsartan) were provided by Takeda Pharmaceuticals International; National Centre for Advancing Translational Sciences clinical and translational science awards; National Institute of General Medical Sciences, Centres of Biomedical Research Excellence award; the Wake Forest Claude Pepper Centre; and the Alzheimer's Association. |
| **Inclusion criteria** | age<br>80 years and older<br><br>blood pressure<br>SBP of 130–180mmHg<br><br>Increased risk for CVD events<br>CKD, defined as an eGFR of 20–59ml/min per 1.73m2, per se was considered a sufficient criterion for increased CVD risk and specifically targeted for recruitment |
| **Exclusion criteria** | Diabetes mellitus<br><br>Proteinuria<br>>1 g/d<br><br>polycystic kidney disease<br><br>cardiovascular criteria<br>prior stroke, symptomatic heart failure, and a left ventricular ejection fraction <35% |

| | |
|---|---|
| | residence in a nursing home<br><br>diagnosis of dementia or use of medications for dementia therapy |
| **Sample size** | 1167 |
| **Interventions** | Intensive versus standard blood pressure control<br>Antihypertensive regimens were adjusted by site investigators to achieve and maintain SBP according to their study group assignment using published algorithms. Use of medications indicated for specific conditions (for example, renin-angiotensin blockers for proteinuric CKD) was encouraged. Healthy lifestyles for BP control and CVD protection (e.g., physical activity) were recommended but not specifically monitored. |
| **Outcome measures** | All-cause mortality<br><br>adverse events<br>Overall adverse events, falls, hypotension, and electrolyte disorders<br><br>eGFR decline<br>≥30% decrease in eGFR |

**Study arms**

**Intensive control (<120mmHg) (N = 586)**

| | |
|---|---|
| % Female | 37.7% |
| Mean age (SD) | 83.3 (SD 3.0) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>60.9 (18.3)<br><br>BP, mean (SD), mm Hg<br>SBP: 142.2 (15.6); DBP 70.0 (11.3) |

| | |
|---|---|
| **Standard control (<140 mmHg) (N = 581)** | |
| % Female | 39.8% |
| Mean age (SD) | 83.7 (SD 3.3) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>59.6 (17.8)<br><br>BP, mean (SD), mm Hg<br>SBP: 142.9 (16.6); DBP 70.0 (11.2) |

## Papademetriou, 2016

| | |
|---|---|
| **Bibliographic Reference** | Papademetriou, Vasilios; Zaheer, Misbah; Doumas, Michael; Lovato, Laura; Applegate, William B; Tsioufis, Costas; Mottle, Amy; Punthakee, Zubin; Cushman, William C; ACCORD Study, Group; Cardiovascular Outcomes in Action to Control Cardiovascular Risk in Diabetes: Impact of Blood Pressure Level and Presence of Kidney Disease.; American journal of nephrology; 2016; vol. 43 (no. 4); 271-80 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the ACCORD trial (ACCORD study group, 2008), using only data for people with CKD. |
| **Study location** | USA and Canada |
| **Study setting** | 77 clinical centres (aggregated within seven networks) across the United States and Canada |
| **Study dates** | recruited between June 2001 and October 2005 |
| **Duration of follow-up** | "The mean duration of follow-up at the time the data and safety monitoring committee recommended the discontinuation of the intensive regimen was 3.5 years (median, 3.4)." |

| | |
|---|---|
| **Sources of funding** | received funding by NHLBI (ClinicalTrials.gov number, NCT00000620). |
| **Inclusion criteria** | blood pressure<br>treated or untreated systolic BP 130–180 mm Hg<br><br>CKD<br>Only participants with CKD stages I-III were included and stages IV and V were excluded. "Stage I CKD was defined as normal eGFR ( ≥ 90 ml/min/1.73 m 2 ) and increased albumin excretion (urine albumin/creatinine ratio ≥ 30 µg/mg). Stage II CKD was defined as eGFR between 60 and 89 ml/min/1.73 m 2 and urine albumin/creatinine ratio ≥ 30 µg/mg. Stage III was defined as eGFR between 30 and 59 ml/min/1.73 m 2 with or without albuminuria. Stage III CKD was further subdivided into CKD IIIA (eGFR 30–44) and CKD IIIB (eGFR 45–59)."<br><br>Diabetes mellitus<br>type 2 diabetes mellitus and a glycated haemoglobin level of 7.5% or more and who either were between the ages of 40 and 79 years and had cardiovascular disease or were between the ages of 55 and 79 years and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidaemia, hypertension, current status as a smoker, or obesity)<br><br>Serum creatinine<br>1.5 mg/dl or less |
| **Exclusion criteria** | frequent or recent serious hypoglycaemic events<br><br>unwillingness to do home glucose monitoring or inject insulin<br><br>BMI<br>>45<br><br>other serious illness |
| **Sample size** | 1,726 |
| **% Female** | 45.0% |
| **Mean age (SD)** | 63.2 (7.3) |
| **Interventions** | Intensive versus standard blood pressure control |

| | |
|---|---|
| | standard antihypertensive therapy (target systolic BP <140 mm Hg) or intensive antihypertensive therapy (target systolic BP <120 mm Hg). |
| **Outcome measures** | All-cause mortality<br><br>Cardiovascular outcomes<br>fatal and non-fatal stroke, non-fatal MI, non-fatal and fatal congestive heart failure, major coronary events, and revascularization |

**Study arms**

| **Intensive target (systolic blood pressure <120 mmHg) (N = 867)** | |
|---|---|
| % Female | 45.3% |
| Mean age (SD) | 63.1 (7.3) years |
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 142.2 (17.0); DBP: 75.7 (11.0)<br><br>CKD stage<br>I: 40.7%, II: 35.5%; III: 23.8%<br><br>Duration of DM, in years<br>12.5 (8.3) |

| **Standard target (systolic blood pressure <140 mmHg) (N = 859)** | |
|---|---|
| % Female | 44.6% |
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 142.8 (16.4); DBP: 75.3 (10.8)<br><br>CKD stage<br>I: 39.6; II: 37.7; III: 22.7<br><br>Duration of DM, in years |

| | |
|---|---|
| | 12.5 (8.4) |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No information

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Probably no

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

No information

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Some concerns

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Probably no

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

**Ruggenenti, 2005**

| | |
|---|---|
| **Bibliographic Reference** | Ruggenenti, Piero; Perna, Annalisa; Loriga, Giacomina; Ganeva, Maria; Ene-Iordache, Bogdan; Turturro, Marta; Lesti, Maria; Perticucci, Elena; Chakarski, Ivan Nediyalkov; Leonardis, Daniela; Garini, Giovanni; Sessa, Adalberto; Basile, Carlo; Alpa, Mirella; Scanziani, Renzo; Sorba, Gianbattista; Zoccali, Carmine; Remuzzi, Giuseppe; REIN-2 Study, Group; Blood-pressure control for renoprotection in patients with |

non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial.; Lancet (London, England); 2005; vol. 365 (no. 9463); 939-46

**Study details**

| | |
|---|---|
| **Study location** | Italy |
| **Study setting** | Multiple centres |
| **Study dates** | June 1999 to June 2003 |
| **Duration of follow-up** | Blood pressure was measured at 1 week, 2 weeks and 3 months after randomization and every 3 months thereafter. Unclear whether there was a planned total duration of follow-up. |
| **Sources of funding** | Supported in part by a grant from Aventis |
| **Inclusion criteria** | Non-diabetic nephropathy<br><br>Persistent proteinuria<br>Urinary protein excretion >1g/24 hours for at least 3 months without evidence of UTI or overt heart failure |
| **Exclusion criteria** | Diabetes mellitus<br>if type 1<br><br>Other<br>suspicion or evidence of: acute MI or cerebrovascular event in prior 6 months, renovascular disease, obstructive uropathy, cancer, collagen disease, higher serum aminotransferase concentrations, chronic cough, history of allergy or poor tolerance of ACE-inhibitors or CCBs,<br><br>received ACE-inhibition therapy within 6 weeks prior to inclusion<br><br>severe uncontrolled hypertension<br><br>medication<br>treatment with NSAIDs, corticosteroids or immunosuppressive drugs<br><br>Drug or alcohol abuse |

| | |
|---|---|
| | pregnancy<br>or breastfeeding, or ineffective contraception |
| **Sample size** | 335 |
| **Loss to follow-up** | 126 participants were not present in the final follow-up. |
| **Interventions** | Intensive versus standard blood pressure control<br>after 6 weeks washout of ACE-inhibitors, Ang-II inhibitors or CCBs, initial baseline measurements were taken via 3 urinary samples. Participants were randomized to standard or intensive BP control. A low-sodium diet and a protein intake of 0.8 g/kg was recommended. Participants were given ramipril 2.5 mg daily, uptitrated to 5mg after a week. Concomitant antihypertensives were given to maintain DBP at <90 mmHg (using minimum possible dose). This was continued for a 6-week run-in phase for all participants. After this point, participants medications were adjusted to reach the target goals (standard or intensive) using a long-acting dihydropyridine CCB. |
| **Outcome measures** | eGFR decline<br>using iohexol clearance, based on at least 3 different measurements. Only those centres capable of performing these measurements provided data on eGFR decline. |

**Study arms**

| | |
|---|---|
| **Intensive BP control (systolic BP <130 mmHg and diastolic BP < 80 mmHg) (N = 167)** | |
| % Female | 26% |
| Mean age (SD) | 54.6 (14.7) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>35.9 (18.6)<br><br>BP, mean (SD), mm Hg<br>SBP: 137.0 (16.7) DBP: 84.3 (9.0) |
| **Standard BP control (diastolic BP < 90 mmHg) (N = 168)** | |

| | |
|---|---|
| % Female | 24% |
| Mean age (SD) | 53.1 (15.8) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>34.1 (18.1)<br><br>BP, mean (SD), mm Hg<br>SBP: 136.4 (17.0); DBP: 83.9 (10.4) |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

Yes

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

Yes

*(Median change in eGFR provided, which could not be analysed in meta-analysis. )*

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

Probably no

*4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?*

Yes

*4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

No information

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Schrier, 2002

| | |
|---|---|
| **Bibliographic Reference** | Schrier R; McFann K; Johnson A; Chapman A; Edelstein C; Brosnahan G; Ecder T; Tison L; Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study.; Journal of the American Society of Nephrology : JASN; 2002; vol. 13 (no. 7) |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | USA |
| **Study setting** | Single Autosomal dominant polycystic kidney disease centre |
| **Study dates** | 1991 - 1994 |
| **Duration of follow-up** | 7 years.<br><br>"Once the BP goal was reached, patients were contacted monthly during the first year and every 2 mo thereafter either by phone or by a GCRC clinic visit to check their BP and review, and if necessary adjust, the medications. In addition, BP was rechecked 1 wk after any medication alteration." |

| | |
|---|---|
| | "Subjects returned to the GCRC every 6 mo during the first 3 yr of the study and then annually for 4 yr more. Each GCRC visit included a history, physical examination, and renal function assessment. Echocardiograms were obtained at baseline and at the 1- and 7-yr visits." |
| **Sources of funding** | "supported by grant 5 P01 DK34039, Human Polycystic Kidney Disease, awarded by the Department of Health and Human Services, Public Health Service, National Institute of Diabetes, Digestive, and Kidney Diseases, and the Clinical Research Center, and grant MORR-00051 from the GCRC Research Program of the Division of Research Resources, National Institutes of Health. Funds were also provided by the Zell Family Foundation. Pfizer Inc. provided funding for part of the study, for up to 3 yr per patient." |
| **Inclusion criteria** | age<br>between 20 and 60 years of age<br><br>blood pressure<br>established hypertension (BP >140/90 mmHg)<br><br>Autosomal dominant polycystic kidney disease<br><br>creatinine clearance<br>>30 ml/min per 1.73 m2<br><br>Left ventricular mass index<br>left ventricular hypertrophy: Men had to have a LVMI >125 g/m2 and women had to have a LVMI >110 g/m2. |
| **Exclusion criteria** | Other<br>"could not tolerate antihypertensive medication withdrawal or could not tolerate the study medications, subjects with 3 g urinary protein per day or those with a second renal diagnosis, subjects who required antiarrhythmic medications, lactating or pregnant subjects or subjects taking oral contraceptive medications, subjects with underlying psychiatric disorders, and subjects who, by the discretion of the investigator, were thought to be unable to comply with the guidelines of the protocol. Additionally, subjects with LVH due to primary causes other than hypertension were excluded from the trial." |
| **Sample size** | 75 included in analysis |
| **% Female** | 45.3% |
| **Mean age (SD)** | Intensive group: 42 (8) years |

| | |
|---|---|
| | Standard group: 40 (8) years |
| **Condition specific characteristics** | BP, mean (SD), mm Hg<br>Intensive group Systolic BP: 143 (15). Standard group Systolic BP: 142 (17). Intensive group Diastolic BP: 95 (11). Standard group Diastolic BP: 96 (11)<br><br>medications used<br>Amlodipine: 40%; enalapril: 60% |
| **Interventions** | Intensive versus standard blood pressure control<br>After the medication washout period, 72 patients were randomized to either enalapril or amlodipine: 36 were randomized to enalapril (escalating dose 5, 10, 20, 40 mg) and 36 to amlodipine (escalating dose 5, 10 mg). However, the randomization to the 2 antihypertensive medications was terminated prematurely after a mean of 2.1 yr of follow-up because funding was lost. More patients thereafter received enalapril, rather than amlodipine, a decision based on physician and patient choice. All subjects were maintained on their standard diets with recommended moderate restriction of sodium intake during the 7-yr study. Eleven subjects from the Denver metropolitan area were initially followed with weekly visits to the GCRC, where dose adjustments were made until the desired BP goal was reached. The remaining 68 subjects were given BP cuffs for home monitoring. |
| **Outcome measures** | acute renal failure<br>end stage renal disease<br><br>eGFR decline |

**Study arms**

**Intensive BP control (<120/80 mmHg) (N = 41)**

| | |
|---|---|
| Condition specific characteristics | medications used<br>Amlodipine: 40%; enalapril: 60% |

**Standard BP control (135 to 140/85 to 90 mmHg) (N = 34)**

| | |
|---|---|
| Condition specific characteristics | medications used<br>Amlodipine: 40%; enalapril: 60% |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No information

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

No information

*(Unclear if ITT was used. )*

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(Unclear if intention to treat analysis was used. )*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

Yes

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Some concerns

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Probably yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*(Analysis method unclear. )*

*Overall Directness*

Directly applicable

**Schrier, 2014**

| | |
|---|---|
| **Bibliographic Reference** | Schrier RW; Abebe KZ; Perrone RD; Torres VE; Braun WE; Steinman TI; Winklhofer FT; Brosnahan G; Czarnecki PG; Hogan MC; Miskulin DC; Rahbari-Oskoui FF; Grantham JJ; Harris PC; Flessner MF; Bae KT; Moore CG; Chapman AB; ; Blood pressure in early autosomal dominant polycystic kidney disease.; The New England journal of medicine; 2014; vol. 371 (no. 24) |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | USA |
| **Study setting** | 7 clinical centres |
| **Study dates** | Enrollment: February 2006 through June 2009. Last study visit was June 2014 |
| **Duration of follow-up** | 5 years.<br><br>Imaging using 1.5-T MRI scanner was conducted at baseline, 24, 48, and 60 months to determine total kidney volume, left-ventricular-mass index, and renal blood flow.<br><br>Central measurements of the serum creatinine level and local measurements of blood urea nitrogen and electrolytes were obtained at all clinical-site visits, and 24-hour urine collections were obtained for central measurements of albumin, sodium, potassium, creatinine, and aldosterone excretion annually. |
| **Sources of funding** | Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases and the National Centre for Research Resources General Clinical Research Centres, National Centre for Advancing Translational Sciences Clinical and Translational Science Awards, by funding from the Zell Family Foundation, and by a grant from the PKD Foundation. |
| **Inclusion criteria** | age<br>15-50 years<br><br>blood pressure<br>hypertension or high-normal blood pressure as defined by a systolic blood pressure of >130mm Hg and/or a diastolic blood pressure of >85mm Hg [61] on three separate readings, or by the current or past use of antihypertensive agents or diuretics for BP control. For subjects aged 15-17, hypertension or high normal blood pressure will be defined as blood pressure exceeding the 75th percentile* for gender averaged across 15–17-year-olds for the 50th percentile of height or by the current use of antihypertensive agents. The values for females are a systolic and/or diastolic blood pressure > 120 / 74 mm Hg and for males, > 125/74 mm Hg. |

| | |
|---|---|
| | eGFR<br>>60 ml/min/1.73 m2, equated from serum creatinine using the 4- variable MDRD equation<br><br>Autosomal Dominant Polycystic Kidney Disease<br>In subjects with a family history, the diagnosis of ADPKD was based on Ravine's Criteria, which requires the presence of at least two renal cysts {unilateral or bilateral} in a subject younger than 30 years; at least two cysts in each kidney among those 30-59 years; and at least four cysts in each kidney among those aged 60 years or older. In the absence of a family history, the diagnosis was based on the presence of at least five renal cysts bilaterally in the absence of findings suggestive of other cystic renal diseases.<br><br>informed consent |
| **Exclusion criteria** | Diabetes mellitus<br>Diabetes requiring insulin or oral hypoglycaemic agents or a fasting serum glucose of >126mg/dl or a random non-fasting glucose of >200 mg/dl, in accordance with ADA recommendations for diagnosis of diabetes<br><br>other serious illness<br>Any serious comorbid condition for which life expectancy is <2 years<br><br>Other<br>Systemic illness with renal involvement; Spot urine albumin-to-creatinine ratio of > 0.5 and/or findings suggestive of kidney disease other than ADPKD; Documented renal vascular disease; Systemic illness with renal involvement; Hospitalization for an acute illness in past 2 months (not including elective admissions); Known presence of undipped cerebral aneurysm >1 cm in diameter.<br><br>medication<br>History of angioneurotic oedema or other hypersensitivity reaction with ACE-I or ARB. Intolerable cough associated with ACE-I will be defined as cough that developed within six months of initiation of ACE-I in the absence of other causes and resolved upon discontinuation of the ACE-I; Contraindication to fi-blocker therapy (e.g. heart block, severe asthma) or other antihypertensive agents from the ordered protocols for Study A; Absolute indication other than hypertension for 6-blocker or calcium channel blocker therapy - (e.g. angina, arrhythmia); Systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications.<br><br>Drug or alcohol abuse<br>History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance that would preclude successful completion of the study<br><br>pregnancy<br>"Currently pregnant or intention of becoming pregnant in the subsequent 5 years. For those who have been pregnant, a minimum of six months post-partum and lactation."<br><br>Heart failure |

| | |
|---|---|
| | Past history of symptomatic or asymptomatic heart failure diagnosed clinically or via cardiac imaging studies (ejection fraction <40% if known) |
| **Sample size** | 558 |
| **Loss to follow-up** | 49 lost to follow-up in the standard BP target arm and 52 were lost to follow-up in the intensive arm. |
| **Interventions** | Intensive versus standard blood pressure control<br>"participants were randomly assigned in a 1:1 ratio to a standard blood-pressure target (120/70 to 130/80mmHg) or a low blood-pressure target (95/60 to 110/75 mm Hg), with stratification according to age, sex, race, baseline estimated GFR, and clinical site." [...] additionally, participants "were randomly assigned in a 1:1 ratio to lisinopril plus telmisartan or lisinopril plus placebo". |
| **Outcome measures** | All-cause mortality<br><br>acute renal failure<br>acute kidney injury<br><br>Cardiovascular outcomes<br>serious cardiovascular or renal events<br><br>eGFR decline |

**Study arms**

**Standard BP target (120/70 to 130/80mmHg) (N = 284)**

140 participants randomized to lisinopril-telmisartan drug combination. 144 participants randomized to lisinopril-placebo drug combination.

| | |
|---|---|
| % Female | 49.6% |
| Mean age (SD) | 36.3 (8.4) years |

| | |
|---|---|
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>91.7 (17.8)<br><br>Race<br>White: 90.8%; Black: 2.5%; Other: 6.3%. |

**Intensive BP target (95/60 to 110/75 mm Hg) (N = 274)**

133 participants randomized to lisinopril-telmisartan drug combination. 141 participants randomized to lisinopril-placebo drug combination.

| | |
|---|---|
| % Female | 48.9% |
| Mean age (SD) | 36.9 (8.2) |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>91.4 (17.2)<br><br>Race<br>White: 94.5%; Black: 2.6%; Other: 3.3% |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

Yes

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Soliman, 2020

| | |
|---|---|
| **Bibliographic Reference** | Soliman, E.Z.; Rahman, A.K.M.F.; Zhang, Z.-M.; Rodriguez, C.J.; Chang, T.I.; Bates, J.T.; Ghazi, L.; Blackshear, J.L.; Chonchol, M.; Fine, L.J.; Ambrosius, W.T.; Lewis, C.E.; Effect of Intensive Blood Pressure Lowering on the Risk of Atrial Fibrillation; Hypertension; 2020; 1491-1496 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the SPRINT trial (Wright 2015), using only data for people with CKD; Study details are reported by Cheung 2017 |

## Toto, 1995

| | |
|---|---|
| **Bibliographic Reference** | Toto RD; Mitchell HC; Smith RD; Lee HC; McIntire D; Pettinger WA; "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis.; Kidney international; 1995; vol. 48 (no. 3) |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | USA |

| | |
|---|---|
| **Study setting** | Not reported |
| **Study dates** | Not reported |
| **Duration of follow-up** | Up to 5 years post-randomization. Patients were followed at 12 week intervals. Additional visits for blood pressure measurement and medication adjustment were performed in an attempt to maintain DBP in the assigned range throughout the follow-up period.<br><br>Glomerular filtration rate and serum creatinine were measured at the following specified intervals: baseline (pre-randomization) and at 3, 9, 12, 18, 24, 36, 42, 48, 54 and 60 months post-randomization. |
| **Sources of funding** | supported by NHLBI RO1-HL23670, NIH GCRC<br>Grant MO1-RR006633 and by a grant from Merck, Sharp and Dohme. |
| **Inclusion criteria** | blood pressure<br>diastolic blood pressure 95 mm Hg or greater, and a history of long-standing hypertension, and without physical or biochemical evidence for a humoral-mediated cause for hypertension.<br><br>Serum creatinine<br>serum creatinine of> 1.6 mg/d<br><br>hypertensive nephrosclerosis<br>with a GFR of 70 ml/min/1.73 m2 or less<br><br>inactive urine sediment<br><br>protein excretion rate of 2 g/day or less |
| **Exclusion criteria** | Diabetes mellitus<br><br>Other<br>Mental incapacity, primary aldosteronism, renovascular hypertension, pheochromocytoma or a recent history (<4 months) of any of the following: malignant hypertension, stroke or myocardial infarction, acute renal failure of any cause, analgesic abuse, polycystic kidney disease, systemic lupus erythematosus, scleroderma, rapidly progressive glomerulonephritis<br><br>pregnancy<br>or lactation<br><br>Hepatic impairment<br>evidence of significant hepatic impairment (AST and ALT greater than 2.5 x normal or serum total bilirubin> 1.5 mg/dl) |

| | |
|---|---|
| | serum creatinine > 7.0 mg/dl |
| **Sample size** | 77 |
| **Loss to follow-up** | 24 participants had a follow-up of less than 36 months. |
| **% Female** | 37.7% |
| **Mean age (SD)** | 55.7 (1.1) |
| **Condition specific characteristics** | eGFR, mean (SD), ml/min per 1.73 m2<br>37.8 (1.8)<br><br>BP, mean (SD), mm Hg<br>Systolic BP: 123 (2); Diastolic BP: 76 (1); Mean arterial BP: 92 (1)<br><br>medications used<br>mean (SD) number of antihypertensive medications used: 2.7 (0.1)<br><br>Race<br>% Black: 75.3% |
| **Interventions** | Intensive versus standard blood pressure control<br>Before randomization, DBP was lowered to 80 mm Hg over a three-to-six-month initial assessment period. To achieve this goal, participants were administered antihypertensive medications using a stepped-care approach as follows: (Step 1) diuretic; (Step 2) n-blocker; (Step 3) hydralazine or minoxidil; and (Step 4) clonidine, a-methyldopa or r1-blocker. In general, the maximum dose of each agent (except diuretic) was used before moving to the next step. Patients went on to be randomized if on three of four consecutive clinic visits the DBP was 80 mm Hg during this period. Participants were randomized to either placebo or enalapril and to either "strict" 65 to 80 mm Hg and "conventional" 85 to 95 mm Hg blood pressure ranges. After randomization, 23 patients in the "strict" and 18 patients in the "conventional" group received enalapril in addition to the stepped-care antihypertensive regimen. The blinded study drug was titrated to the maximum allowable dose and the unblinded antihypertensive(s) were back-titrated as needed to achieve and maintain blood pressure control. |
| **Outcome measures** | All-cause mortality<br><br>acute renal failure |

| | |
|---|---|
| | data presented for 50% decline in GFR or 4 5 9 doubled serum creatinine (from baseline) and for the number of participants with end stage renal disease.<br><br>eGFR decline<br>The rate of decline in GFR (GFR slope in ml/minhl.73 m2/year) was the primary outcome measure in this study. At least three GFR measurements were considered necessary to calculate a valid GFR slope and all patients met this criterion (mean = 7, range 3 to 11). The rate of decline in GFR for each group was estimated by the method of maximum likelihood in a mixed effects model which takes into account differences in duration of follow- up among patients [29]. The estimated decline in GFR was also calculated by the model after accounting for potential predictors of declining GFR at baseline including age, race, gender, serum creatinine and 24-hour urine protein excretion rate. The study also evaluated the rate of change in GFR using a piece-wise two-slope linear model in which the effect of the first three months of (post-randomization) intervention on the overall change in GFR within study groups was evaluated. Subgroup analysis for eGFR decline is presented by race (black versus non-black participants) |

**Study arms**

**Intensive blood pressure control (DBP 65 to 80 mmHg) (N = 42)**

| | |
|---|---|
| % Female | 47.6% |
| Mean age (SD) | 55.8 (1.5) |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>34.6 (2.3)<br><br>BP, mean (SD), mm Hg<br>Systolic blood pressure: 124 (2); Diastolic blood pressure: 76 (1) ;Mean arterial pressure: 92 (1)<br><br>medications used<br>Mean (SD) number of antihypertensive medications used: 2.7 (0.2)<br><br>Race<br>% Black: 69.0% |

**Standard blood pressure control (DBP 85 to 95 mmHg) (N = 35)**

| | |
|---|---|
| % Female | 25.7% |
| Mean age (SD) | 55.7 (1.6) |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>41.9 (3.1)<br><br>BP, mean (SD), mm Hg<br>Systolic BP: 122 (3); Diastolic BP: 77 (1); Mean arterial BP: 92 (2)<br><br>medications used<br>Mean (SD) number of antihypertensive medications used: 2.6 (0.2)<br><br>Race<br>% Black: 82.9% |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

Yes

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Probably yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

No information

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Vaduganathan, 2020

| | |
|---|---|
| **Bibliographic Reference** | Vaduganathan, M.; Pareek, M.; Kristensen, A.M.D.; Biering-Sorensen, T.; Byrne, C.; Almarzooq, Z.; Olesen, T.B.; Olsen, M.H.; Bhatt, D.L.; Prevention of heart failure events with intensive versus standard blood pressure lowering across the spectrum of kidney function and albuminuria: a SPRINT substudy; European Journal of Heart Failure; 2020 |

**Study details**

| | |
|---|---|
| **Study type** | Post-hoc analysis of a randomised controlled trial (RCT)<br>Post-hoc analysis of the SPRINT trial (Wright 2015), using only data for people with CKD; Study details are reported by Cheung 2017 |

## Wright, 2002

| | |
|---|---|
| **Bibliographic Reference** | Wright, Jackson T Jr; Agodoa, Lawrence; Contreras, Gabriel; Greene, Tom; Douglas, Janice G; Lash, James; Randall, Otelio; Rogers, Nancy; Smith, Michael C; Massry, Shaul; African American Study of Kidney Disease and Hypertension Study, Group; Successful blood pressure control in the African American Study of Kidney Disease and Hypertension.; Archives of internal medicine; 2002; vol. 162 (no. 14); 1636-43 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | United States |
| **Study setting** | Not reported, but multicentre |
| **Study dates** | June 1995 to September 2001 |

| | |
|---|---|
| **Duration of follow-up** | Average follow-up 3 to 6 years.<br><br>"Participants were seen every 2 months, and feedback was provided to them concerning their blood pressure, blood pressure goals, and medication consumption (pill counts). In addition, participants whose blood pressures were more than 5 mm Hg above their MAP goal at 2 consecutive visits were required by protocol to be seen within 2 weeks." |
| **Sources of funding** | National Institute of Diabetes and Digestive and Kidney Diseases (part funded by Pfizer, Astra-Zeneca and King pharmaceuticals)<br><br>National Institutes of Health<br><br>National Centre on Minority Health and Health Disparities. |
| **Inclusion criteria** | age<br>18 - 70 years<br><br>blood pressure<br>diastolic BP of 95mm Hg or more<br><br>CKD<br>renal insufficiency defined by iothalamate-determined GFR between 20 and 65 mL/min per 1.73 m2, and no other identified causes of renal insufficiency.<br><br>Race<br>self-identified African American |
| **Exclusion criteria** | Criteria 1<br>Accelerated or malignant hypertension within 6 months<br><br>Criteria 2<br>Evidence of non-blood pressure related causes of kidney disease<br><br>Diabetes mellitus<br>history of type 1 or 2 diabetes, fasting glucose >= 140mg/dL or random glucose level >200mg/dL<br><br>Proteinuria<br>Urinary protein creatinine ratio >2.5 |

| | |
|---|---|
| | cardiovascular criteria<br>Clinical congestive heart failure<br><br>other serious illness<br>Serious systemic disease<br><br>Other<br>Specific indication for, or contraindication to, one of the included antihypertensives or study procedures. |
| **Sample size** | 1094 |
| **% Female** | 39% |
| **Mean age (SD)** | 54.5 (10.7) years |
| **Condition specific characteristics** | medications used<br>mean of 2.4 antihypertensive medications used<br><br>Hypertension (%)<br>100%. Average reported duration was 14 years<br><br>GFR, mean (SD), ml/min per 1.73 m2<br>45.7 (13.0) |
| **Interventions** | Intensive versus standard blood pressure control<br>"Participants were randomized to a goal blood pressure based on MAP of either 102 to 107 mm Hg (usual MAP goal) or 92 mm Hg or less (low MAP goal). In participants randomized to the usual MAP goal, if systolic blood pressure was 160 mm Hg or more, systolic blood pressure was reduced to below this level, even if MAP decreased to less than 102 mm Hg." [...] "In addition, participants were also randomized (double-blind) to an antihypertensive regimen containing sustained-release metoprolol succinate (50-200 mg/d) (Toprol XL; Astra-Zeneca Pharmaceuticals, Wayne, Pa), ramipril (2.5-10 mg/d) (Altace; King Pharmaceuticals, Bristol, Tenn), or amlodipine besylate (2.5-10 mg/d) (Norvasc; Pfizer, Inc, New York, NY). " [...]"If the blood pressure goal was not achieved, additional agents were added in the following recommended order: furosemide, doxazosin, clonidine hydrochloride, or hydralazine hydrochloride (or minoxidil, if needed)." [...] "The dosage of each agent (including the blinded agents) was titrated to the maximum tolerated dose before the addition of a subsequent agent. In those participants randomized to the usual MAP goal and whose MAP fell below 102 mm Hg, the use of antihypertensive drugs was reduced, starting with the most recently added agent." |
| **Outcome measures** | All-cause mortality |

| | |
|---|---|
| | reported in Ku (2017)<br><br>acute renal failure<br>End-stage renal disease reported in Ku (2017)<br><br>eGFR decline<br>reported in Lewis (2004) |

**Study arms**

**Standard MAP (102=107 mmHg) (N = 554)**

| | |
|---|---|
| Duration of follow-up | Average follow-up 3 to 6 years |
| Inclusion criteria | Criteria 1<br>self-identified African American<br><br>Criteria 2<br>iothalamate determined GFR 20 - 65 mL/min per 1.73m^2<br><br>age<br>18 - 70 years<br><br>blood pressure<br>diastolic BP of 95mm Hg or more |
| % Female | 40% |
| Mean age (SD) | 54.5 (10.4) |
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 149 (23); DBP: 95 (14); MAP: 113 (15)<br><br>Hypertension (%)<br>100%. Mean (SD) duration of hypertension: 14 (10) years<br><br>GFR, mean (SD), ml/min per 1.73 m2 |

| | |
|---|---|
| | 45.3 (13.2) |

**Low MAP (92 mmHg or less) (N = 540)**

| | |
|---|---|
| % Female | 38% |
| Mean age (SD) | 54.4 (10.9) years |
| Condition specific characteristics | BP, mean (SD), mm Hg<br>SBP: 152 (25); DBP: 96 (15); MAP: 115 (17)<br><br>Hypertension (%)<br>100%. Mean (SD) reported duration was 14 (11) years<br><br>GFR, mean (SD), ml/min per 1.73 m2<br>46.1 (12.8) |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

Probably yes

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Probably yes

*(No information regarding study power estimation, but assumed to be undertaken. )*

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

No

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Wuhl, 2004

| | |
|---|---|
| **Bibliographic Reference** | Wuhl, Elke; Mehls, Otto; Schaefer, Franz; ESCAPE Trial, Group; Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure.; Kidney international; 2004; vol. 66 (no. 2); 768-76 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | 13 European countries |
| **Study setting** | 33 paediatric nephrology units |
| **Study dates** | 1998 - 2006 |
| **Duration of follow-up** | During the 5-year study period, blood pressure measured in the outpatient clinic with the use of auscultatory or oscillometric techniques, glomerular filtration rate, and urinary protein excretion were assessed every 2 months, and ambulatory blood-pressure monitoring was performed every 6 months. Results are reported in Wuhl (2004) at 6 months and in ESCAPE (2009) at 5 years. |
| **Sources of funding** | "<br><br>Supported by grants from the Boehringer Ingelheim Stiftung; the European Commission (Fifth Framework Programme, QLRT-2001-00908); Kuratorium für Dialyse und Nierentransplantation, Neu-Isenburg; and the Baxter Extramural Grant Program.<br><br>Dr. Montini reports receiving grant support from AstraZeneca; and Dr. Schaefer, consulting fees from Novartis, AstraZeneca, and Boehringer Ingelheim and grant support from Novartis and AstraZeneca. No other potential conflicts of interest relevant to this article were reported." |
| **Inclusion criteria** | age<br>aged 3 to 18 years<br><br>blood pressure<br>"high normal or elevated blood pressure". Participants had a 24-hour mean arterial pressure greater than the 50th percentile for height and/or receiving antihypertensive medication |

| | |
|---|---|
| | CKD<br>mild to moderate CRF (initial GFR 15 to 80 mL/ min/1.73m2) |
| **Exclusion criteria** | Other<br>in an unstable clinical condition, or had major primary cardiac, hepatic, or gastrointestinal disorders. Participants were withdrawn if serious adverse events occurred, if a major concomitant disease developed, if they were obviously noncompliant with the protocol, or if they requested to be withdrawn.<br><br>medication<br>receiving immunosuppressive treatment including glucocorticoids |
| **Sample size** | 468 entered the run-in phase. 385 met inclusion criteria at point of randomization. |
| **Loss to follow-up** | 83 participants were lost during the run-in period (prior to randomization). Following randomization, 13 patients (7 in the group that received intensified blood-pressure control and 6 in the group that received conventional blood-pressure control) were withdrawn from the study during the 2-month period in which the dose of ramipril was increased to the maximum dose.<br><br>During the course of the study, 92 patients (46 in each group) were withdrawn before reaching the primary end point; the reasons for withdrawal included transition to adult units (49 patients), patient's request (12), nonadherence with taking the study medication (12), hyperkalaemia (7), hypotension (2), and other adverse events (10). |
| **Interventions** | Intensive versus standard blood pressure control<br>Participants were enrolled in a six-month run-in period. In all patients on prevalent ACE inhibitor therapy, this medication was discontinued at least two months before the end of the run-in period. During this wash-out period, blood pressure was controlled by home and casual BP measurements and, if necessary, antihypertensive medication was adjusted by adding non-RAS antagonists to maintain a blood pressure in the normal range. were randomized to either conventional or intensified BP targets, aiming for the 50th to 95th or below the 50th percentile of 24-hour mean arterial pressure (MAP) for height and gender, respectively. Participants were started on ramipril (6 mg/m2 body surface area in tablets of 1.25, 2.5, or 5 mg as a single morning dose). The decision whether concomitant antihypertensive medication was reduced, unchanged, or increased around the time of randomization and start of ramipril was at the discretion of the responsible physician. |

**Study arms**

| | |
|---|---|
| **Standard blood pressure control (50th to 90th percentile of 24-hour mean arterial pressure) (N = 196)** | |
| % Female | 62.2% |
| Mean age (SD) | 11.5 (4.0) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>45.4 (19.9)<br>BP, mean (SD), mm Hg<br>24 hour mean arterial pressure: 89.5 (9.5)<br>medications used<br>10% used 2 or more, and 23% used 1, antihypertensive treatment in addition to ramipril<br>Mean (SD) duration of CKD<br>6.7 (4.5)<br>Underlying renal disorder<br>12% glomerulopathies, 71% hypoplasia-dysplasia, 17% other |
| Outcome measures | All-cause mortality<br>acute renal failure<br>50% reduction in the glomerular filtration rate or progression to end-stage renal disease (glomerular filtration rate <10 ml per minute per 1.73 m2 or start of renal-replacement therapy). Since an acute decrease in the glomerular filtration rate (<25% decrease) is expected after the start of ACE-inhibitor therapy,13 the glomerular filtration rate that was recorded 2 months after the initiation of ramipril was used as a baseline for the analysis of the reduction in the glomerular filtration rate over time.<br>Cardiovascular outcomes<br>changes in blood pressure<br>eGFR decline |
| Intensive blood pressure control (<50th percentile of 24-hour mean arterial pressure) (N = 189) | |
| % Female | 56.6% |
| Mean age (SD) | 11.5 (4.1) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>46.4 (19.1)<br>BP, mean (SD), mm Hg<br>24 hour mean arterial pressure: 89.5 (10.3) |

| Standard blood pressure control (50th to 90th percentile of 24-hour mean arterial pressure) (N = 196) | |
|---|---|
| % Female | 62.2% |
| Mean age (SD) | 11.5 (4.0) years |
| Condition specific characteristics | eGFR, mean (SD), ml/min per 1.73 m2<br>45.4 (19.9)<br>BP, mean (SD), mm Hg<br>24 hour mean arterial pressure: 89.5 (9.5)<br>medications used<br>10% used 2 or more, and 23% used 1, antihypertensive treatment in addition to ramipril<br>Mean (SD) duration of CKD<br>6.7 (4.5)<br>Underlying renal disorder<br>12% glomerulopathies, 71% hypoplasia-dysplasia, 17% other |
| Outcome measures | All-cause mortality<br>acute renal failure<br>50% reduction in the glomerular filtration rate or progression to end-stage renal disease (glomerular filtration rate <10 ml per minute per 1.73 m2 or start of renal-replacement therapy). Since an acute decrease in the glomerular filtration rate (<25% decrease) is expected after the start of ACE-inhibitor therapy,13 the glomerular filtration rate that was recorded 2 months after the initiation of ramipril was used as a baseline for the analysis of the reduction in the glomerular filtration rate over time.<br>Cardiovascular outcomes<br>changes in blood pressure<br>eGFR decline |
| | medications used<br>14% used 2 or more, and 19% used 1, antihypertensive treatment in addition to ramipril<br>Mean (SD) duration of CKD<br>6.4 (4.4) years<br>Underlying renal disorder<br>14% glomerulopathies, 66% hypoplasia-dysplasia, 20% other |

**Domain 1: Bias arising from the randomisation process**

*1. 1. Was the allocation sequence random?*

Yes

*1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?*

No information

*1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?*

No

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?*

No/Probably no

*2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?*

Yes

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*2.1. Were participants aware of their assigned intervention during the trial?*

No information

*2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?*

No information

*2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?*

Yes

*2.4. Could failures in implementing the intervention have affected the outcome?*

Yes

*2.5. Did study participants adhere to the assigned intervention regimen?*

Yes

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*3.1 Were data for this outcome available for all, or nearly all, participants randomised?*

Yes

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*4.1 Was the method of measuring the outcome inappropriate?*

Yes

*4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?*

No

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?*

Yes

*5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?*

No/Probably no

*5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?*

No/Probably no

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

# Appendix F – Forest plots

### Scales for forest plot outcomes

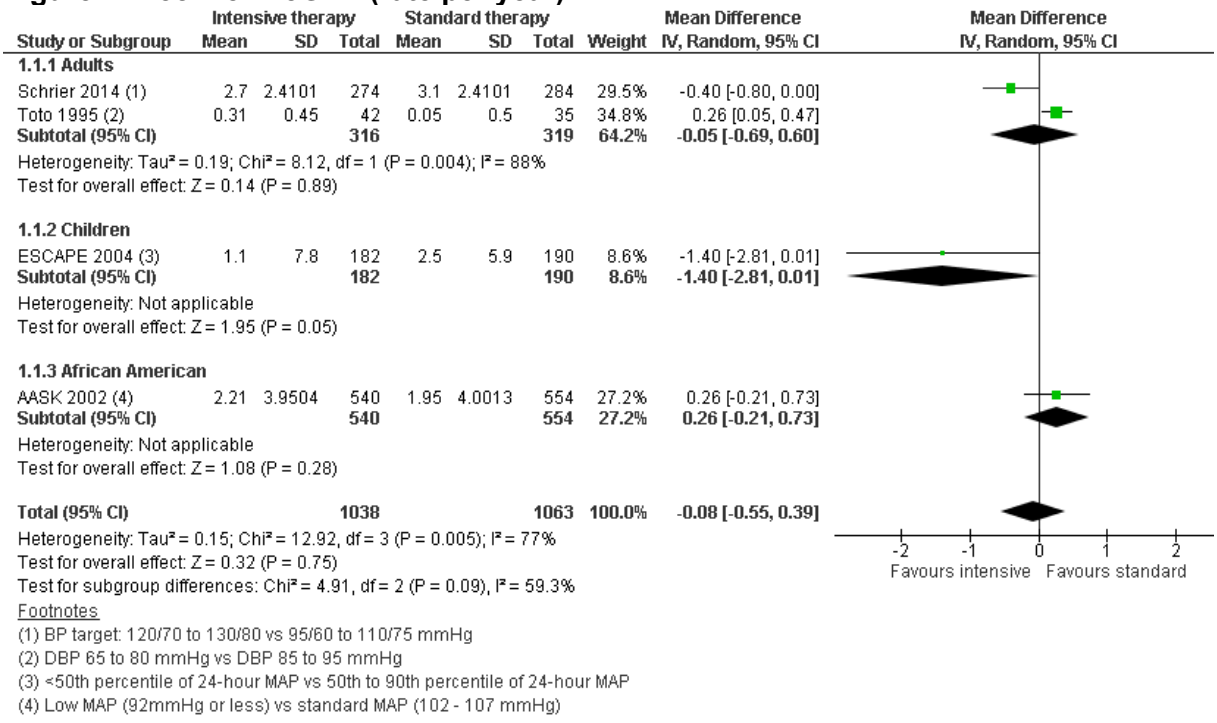
Mean difference – higher value (above zero) favours standard BP

Hazard Ratio – higher value (above 1) favours standard BP

Relative Risk - higher value (above 1) favours standard BP

### Intensive blood pressure target versus standard target

**Figure 1: Decline in eGFR (rate per year)**




Footnotes

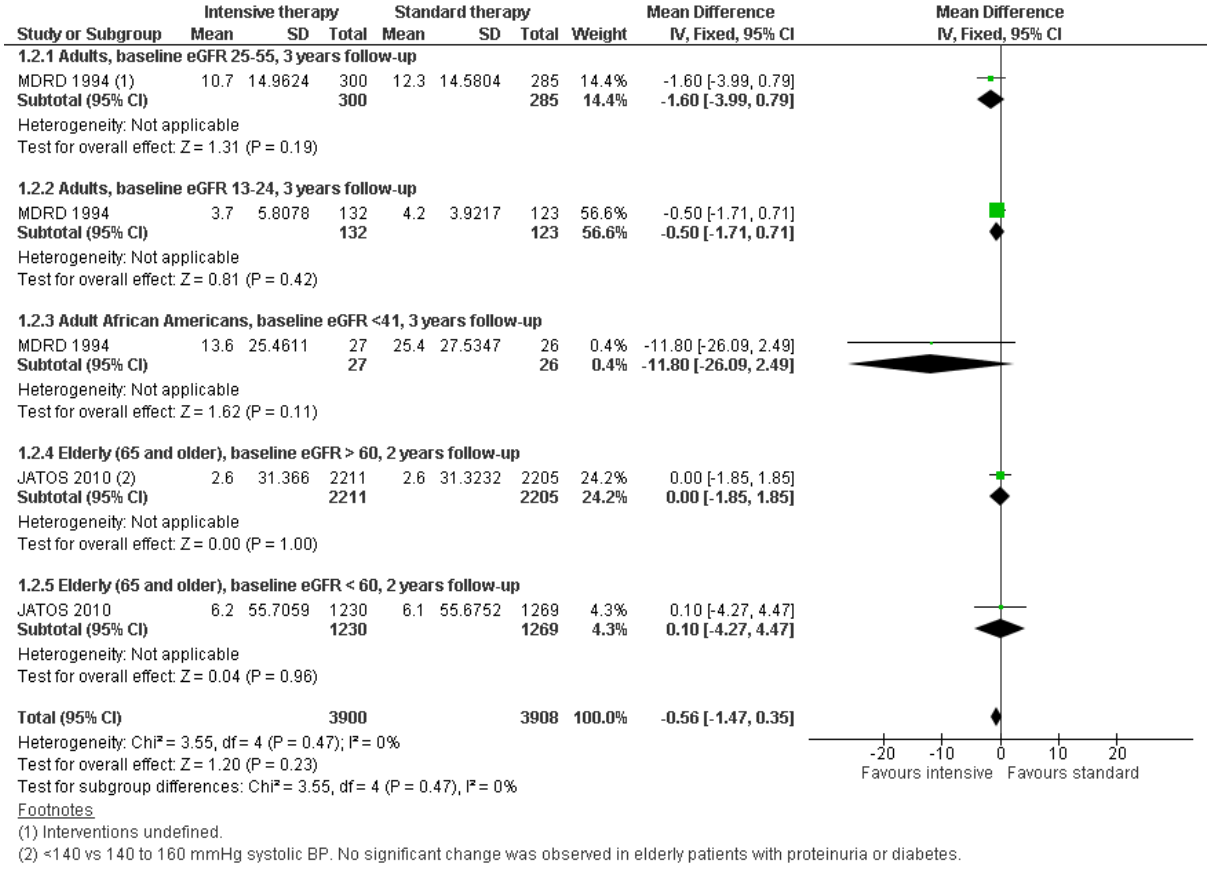
(1) BP target: 120/70 to 130/80 vs 95/60 to 110/75 mmHg

(2) DBP 65 to 80 mmHg vs DBP 85 to 95 mmHg

(3) <50th percentile of 24-hour MAP vs 50th to 90th percentile of 24-hour MAP

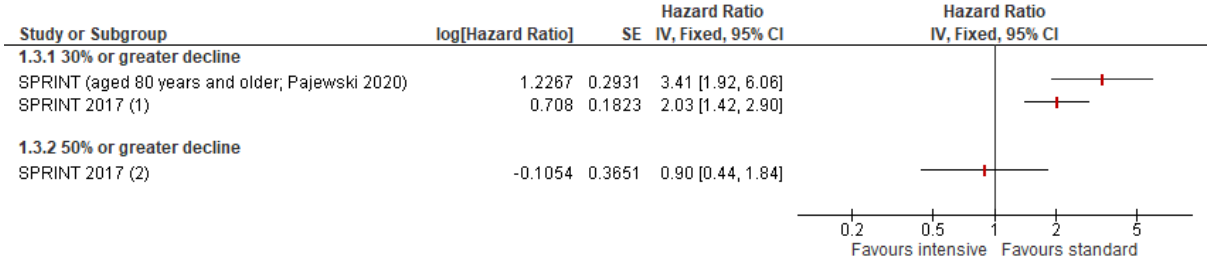
(4) Low MAP (92mmHg or less) vs standard MAP (102 - 107 mmHg)

## Figure 2: Decline in eGFR (change from baseline)




Footnotes
(1) Interventions undefined.
(2) <140 vs 140 to 160 mmHg systolic BP. No significant change was observed in elderly patients with proteinuria or diabetes.

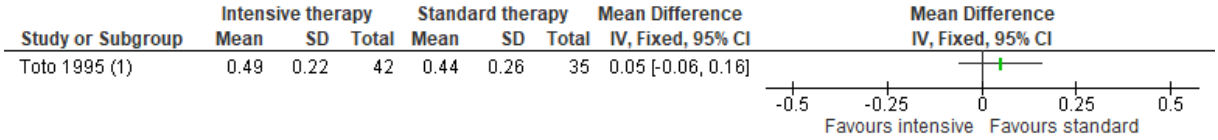
## Figure 3: Percentage decline in eGFR (rate per year)




Footnotes
(1) 120 vs 140 mmHg target systolic BP
(2) There was also no difference in the rate of 40% or greater eGFR.

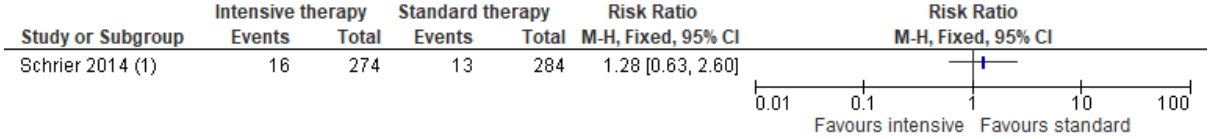
*Higher rate of eGFR decline in intensive group due to the acute (up to 6 months) effect of the intervention. eGFR results from 6 months onwards showed no difference when compared to standard treatment.*

**Figure 4: Decline in serum creatinine (rate per year)**



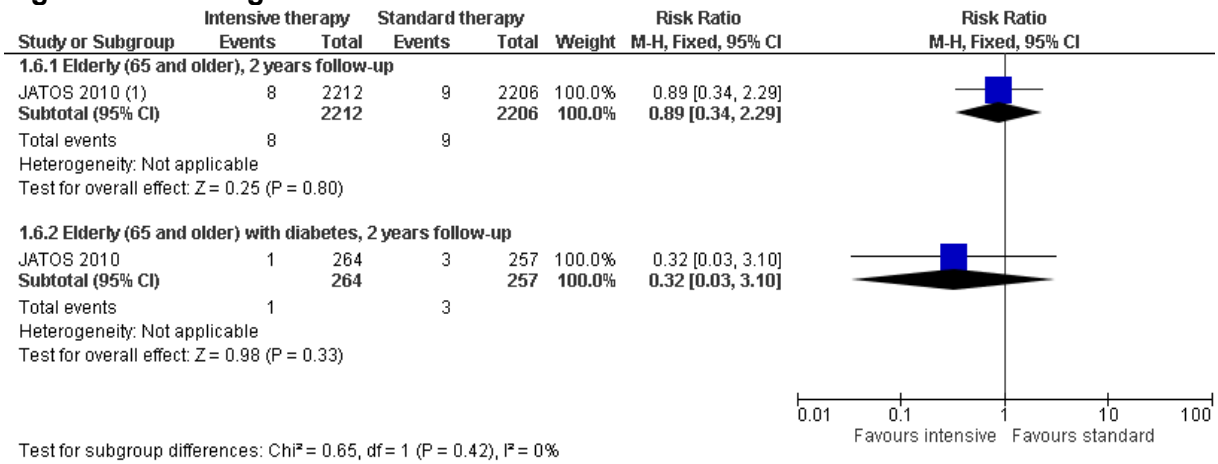

Footnotes
(1) Target DBP 65 to 80 mmHg vs DBP 85 to 95 mmHg.

**Figure 5: Elevated serum creatinine, 0.3 mg per decilitre or more (acute kidney injury), 5 years follow-up**




Footnotes
(1) BP target: 120/70 to 130/80 vs 95/60 to 110/75 mmHg

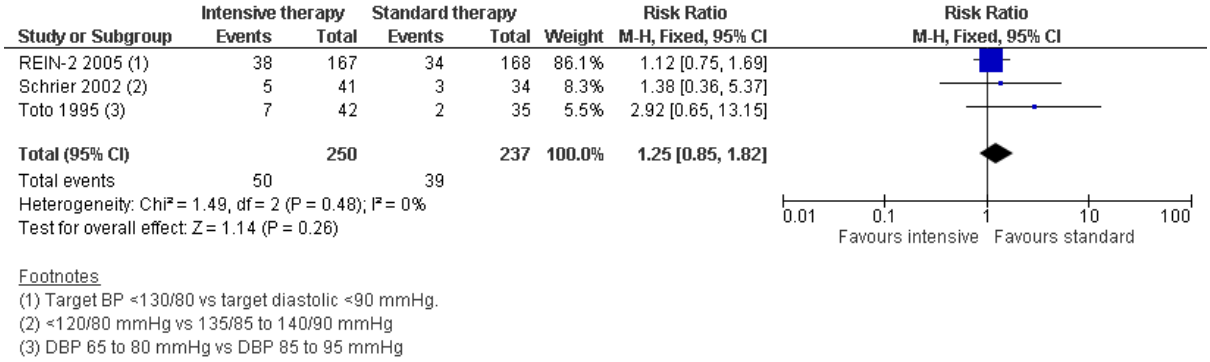
**Figure 6: Doubling of serum creatinine or ESRD**




Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%

Footnotes
(1) Target systolic BP <140 vs 140 to 160 mmHg.

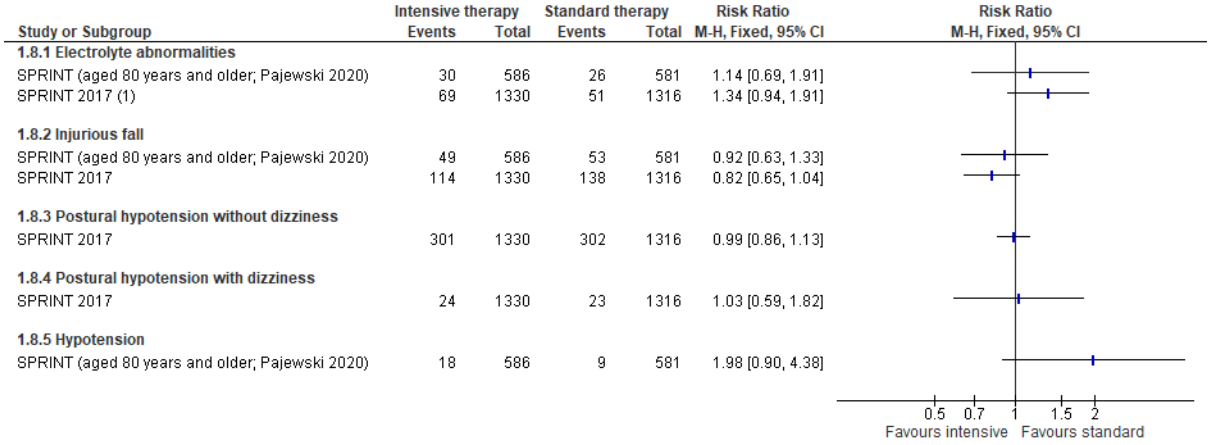
## Figure 7: Progression to ESRD, up to 7 years follow-up




Footnotes
(1) Target BP <130/80 vs target diastolic <90 mmHg.
(2) <120/80 mmHg vs 135/85 to 140/90 mmHg
(3) DBP 65 to 80 mmHg vs DBP 85 to 95 mmHg

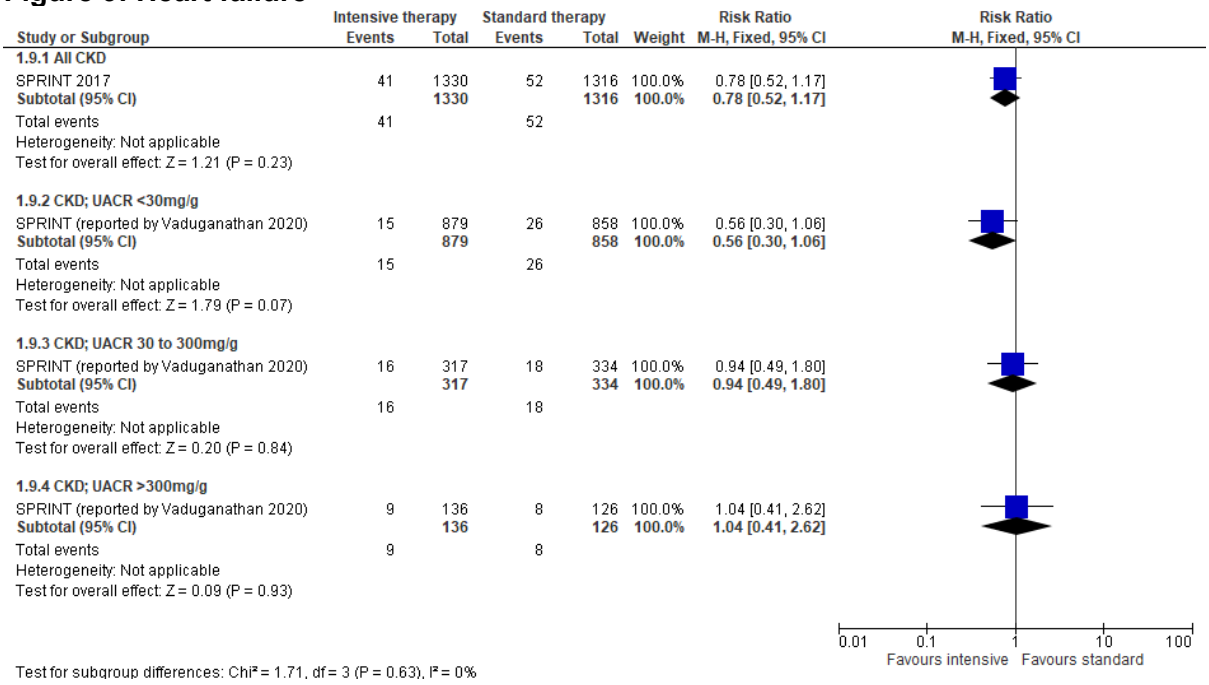
*High serum creatinine, mean arterial blood pressure and high systolic blood pressure were significantly associated with increased risk of ESRD.*

## Figure 8: Adverse events



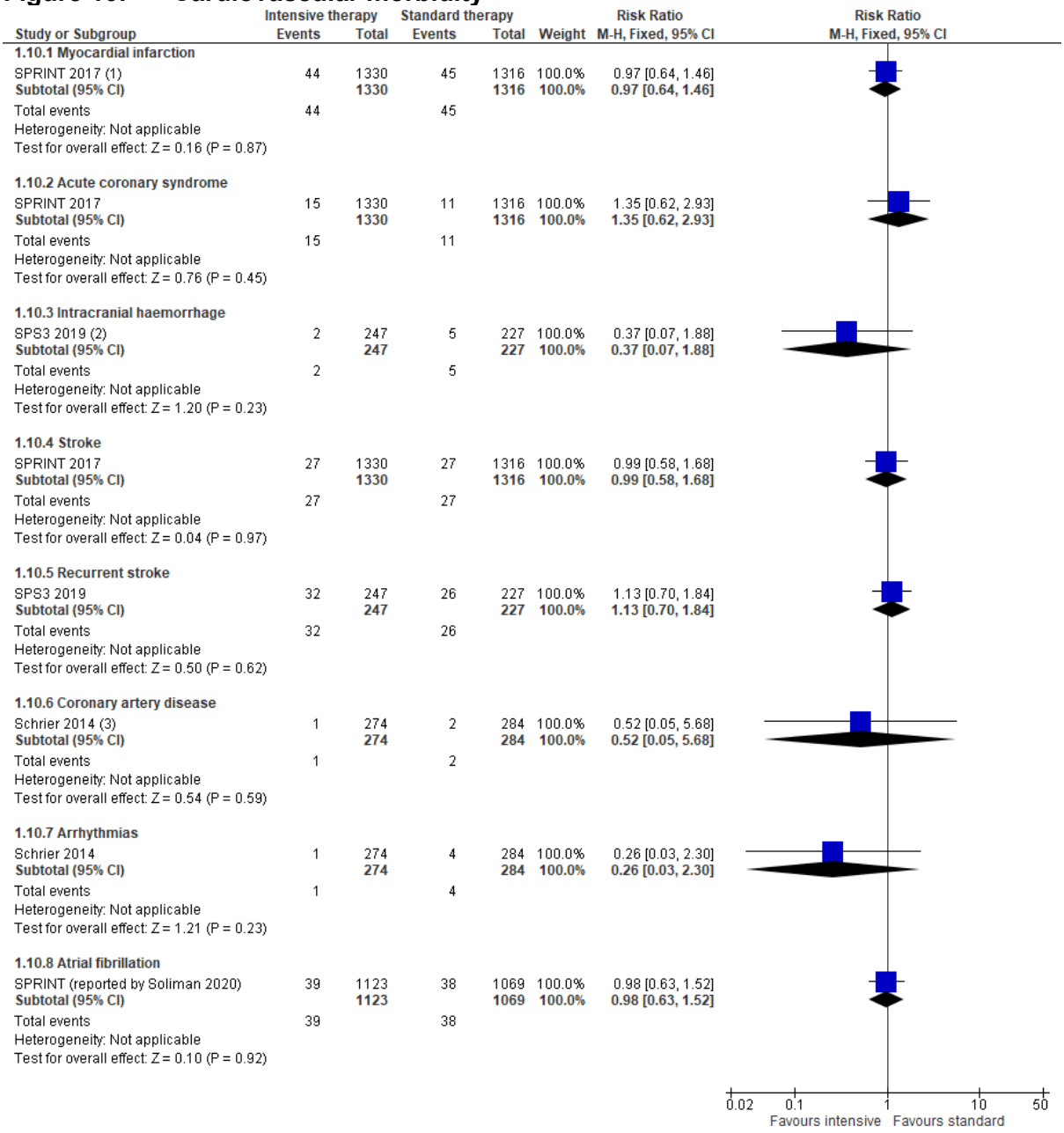

Footnotes
(1) 120 vs 140 systolic BP.

**Figure 9: Heart failure**



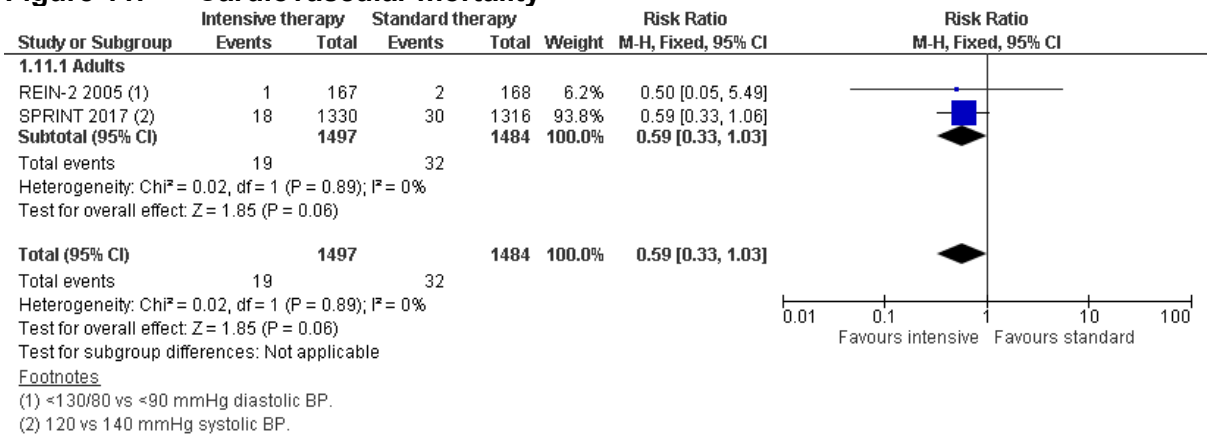

*UACR: urinary albumin:creatinine ratio*

**Figure 10: Cardiovascular morbidity**




Footnotes
(1) 120 vs 140 systolic BP.
(2) <130 mmHg vs 130-149 mmHg systolic BP
(3) 120/70 to 130/80 vs 95/60 to 110/75 mmHg

## Figure 11: Cardiovascular mortality

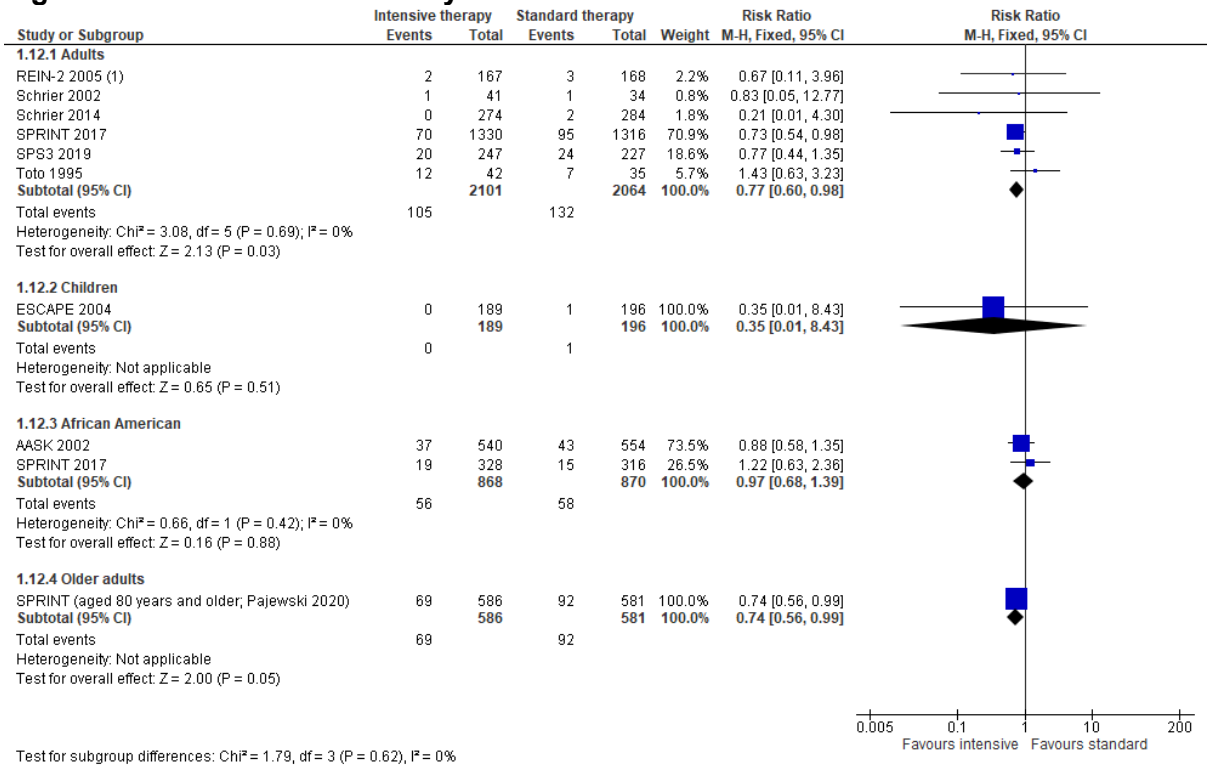



Footnotes

(1) <130/80 vs <90 mmHg diastolic BP.

(2) 120 vs 140 mmHg systolic BP.

## Figure 12: All-cause mortality

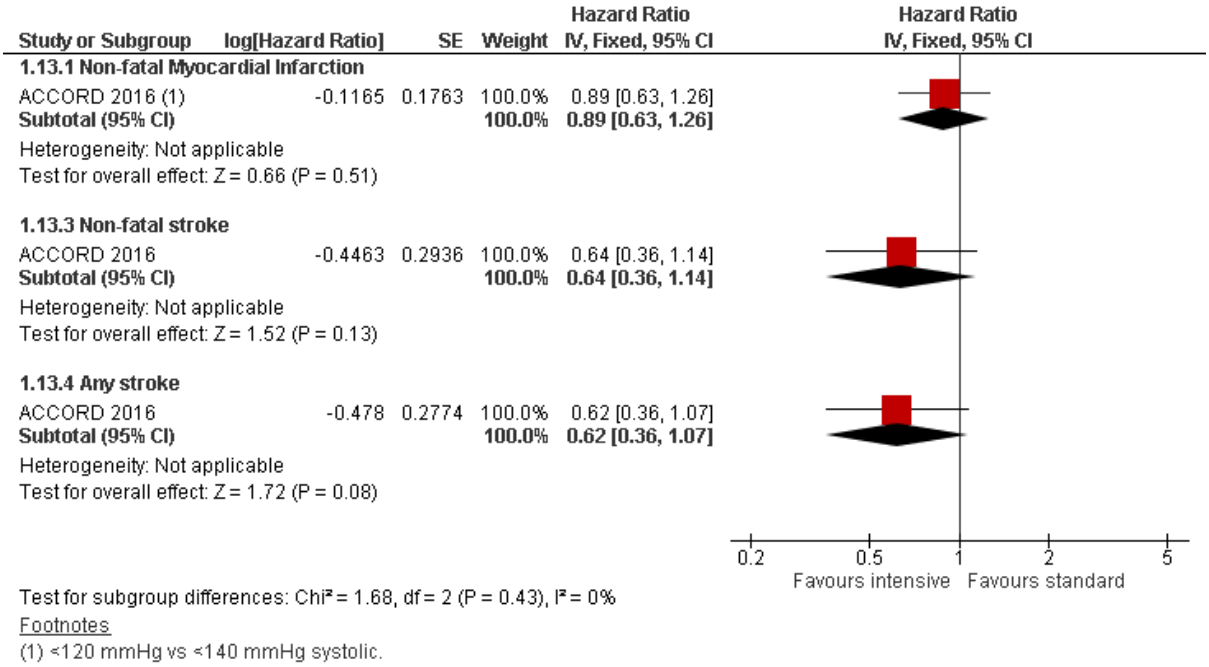



Test for subgroup differences: Chi² = 1.79, df = 3 (P = 0.62), I² = 0%

Footnotes

(1) High serum creatinine, mean arterial blood pressure and high systolic blood pressure were significantly associated with increased risk of ESRD.

**Figure 13: Cardiovascular morbidity (rate per year) in Type 2 diabetes, mean 3.5 years follow-up**

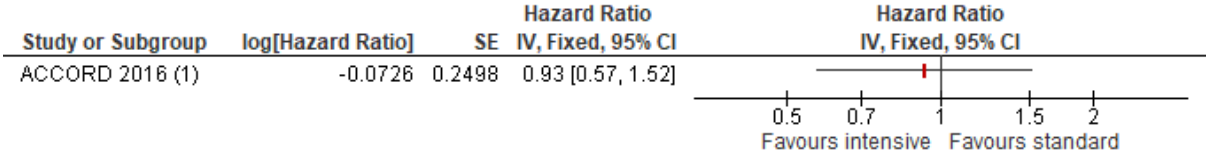



Test for subgroup differences: Chi² = 1.68, df = 2 (P = 0.43), I² = 0%

Footnotes

(1) <120 mmHg vs <140 mmHg systolic.

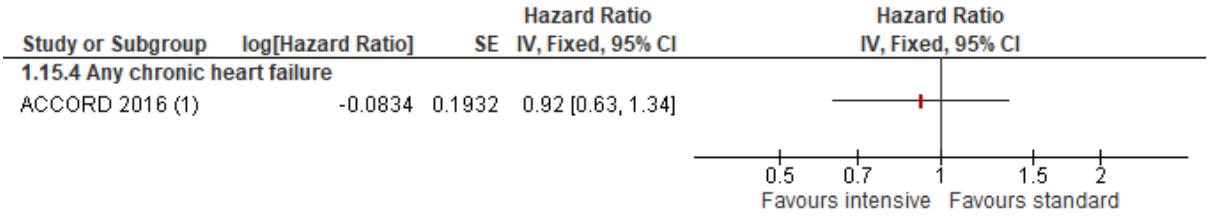
**Figure 14: Cardiovascular mortality (rate per year) in Type 2 diabetes, mean 3.5 years follow-up**




Footnotes

(1) <120 mmHg vs <140 mmHg systolic.

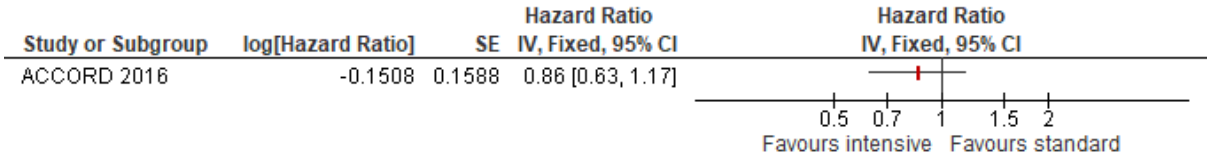
**Figure 15: Chronic heart failure (rate per year) in Type 2 diabetes, mean 3.5 years follow-up**




Footnotes

(1) <120 mmHg vs <140 mmHg systolic.

**Figure 16: All cause mortality (rate per year) in Type 2 diabetes, mean 3.5 years follow-up**



# Appendix G – GRADE tables

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive BP therapy versus standard BP therapy | Control | Relative (95% CI) | Absolute | |
| **Decline in eGFR (rate per year) (Better indicated by lower values) [MID = 1.60]** | | | | | | | | | | | |
| 4 | randomised trials | no serious risk of bias | very serious[1] | no serious indirectness | no serious imprecision | none | 1038 | 1063 | - | MD 0.08 lower (0.55 lower to 0.39 higher) | LOW |
| **Decline in eGFR (rate per year) - Adults (Better indicated by lower values) [MID = 0.73]** | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | very serious[1] | no serious indirectness | serious[2] | none | 316 | 319 | - | MD 0.05 lower (0.69 lower to 0.6 higher) | VERY LOW |
| **Decline in eGFR (rate per year) - Children (Better indicated by lower values) [MID = 2.95]** | | | | | | | | | | | |
| 1[3] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 182 | 190 | - | MD 1.4 lower (2.81 lower to 0.01 higher) | HIGH |
| **Decline in eGFR (rate per year) - African American (Better indicated by lower values) [MID = 2.00]** | | | | | | | | | | | |
| 1[5] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 540 | 554 | - | MD 0.26 higher (0.21 lower to 0.73 higher) | HIGH |
| **Decline in eGFR (change from baseline) (follow-up 2 to 3 years; Better indicated by lower values) [MID = 13.97]** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 3900 | 3908 | - | MD 0.56 lower (1.47 lower to 0.35 higher) | HIGH |
| **Decline in eGFR (change from baseline) - Baseline eGFR 25-55, 3 years follow-up (Better indicated by lower values) [MID = 7.29]** | | | | | | | | | | | |
| 1[6] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 300 | 285 | - | MD 1.6 lower (3.99 lower to 0.79 higher) | HIGH |
| **Decline in eGFR (change from baseline) - Baseline eGFR 13-24, 3 years follow-up (Better indicated by lower values) [MID = 1.96]** | | | | | | | | | | | |
| 1[6] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 132 | 123 | - | MD 0.5 lower (1.71 lower to 0.71 higher) | HIGH |
| **Decline in eGFR (change from baseline) - African American, 3 years follow-up (Better indicated by lower values) [MID = 13.77]** | | | | | | | | | | | |
| 1[6] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[2] | none | 27 | 26 | - | MD 11.8 lower (26.09 lower to 2.49 higher) | MODERATE |
| **Decline in eGFR (change from baseline) - Elderly (65 and older) at 2 years follow-up, eGFR > 60 (Better indicated by lower values) [MID = 15.66]** | | | | | | | | | | | |
| 1[7] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 2211 | 2205 | - | MD 0 higher (1.85 lower to 1.85 higher) | HIGH |
| **Decline in eGFR (change from baseline) - Elderly (65 and older) at 2 yeas follow-up, eGFR < 60 (Better indicated by lower values) [MID = 27.84]** | | | | | | | | | | | |
| 1[7] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 1230 | 1269 | - | MD 0.1 higher (4.27 lower to 4.47 higher) | HIGH |
| **% decline in eGFR (rate per year) - 30% or greater decline** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 92/1330 (6.9%) | 44/1316 (3.3%) | HR 2.03 (1.42 to 2.9) | 33 more per 1000 (from 14 more to 60 more) | HIGH |
| **% decline in eGFR (rate per year) - 30% or greater decline (adults 80 years and older)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 48/586 (8.2%) | 17/581 (2.9%) | HR 3.41 (1.92 to 6.06) | 67 more per 1000 (from 26 more to 135 more) | HIGH |
| **% decline in eGFR (rate per year) - 50% or greater decline** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 15/1330 (1.1%) | 16/1316 (1.2%) | HR 0.9 (0.44 to 1.84) | 1 fewer per 1000 (from 7 fewer to 10 more) | MODERATE |
| **Decline in serum creatinine (rate per year) (follow-up 5 years; Better indicated by lower values) [MID = 0.14]** | | | | | | | | | | | |
| 1[11] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[2] | none | 42 | 35 | - | MD 0.05 higher (0.06 lower to 0.16 higher) | MODERATE |
| **Elevated serum creatinine, 0.3 mg per deciliter or more (acute kidney injury)** | | | | | | | | | | | |
| 1[12] | randomised trials | no serious risk of bias | no serious inconsistency[4] | serious[13] | very serious[14] | none | 16/274 (5.8%) | 13/284 (4.6%) | RR 1.28 (0.63 to 2.6) | 13 more per 1000 (from 17 fewer to 73 more) | VERY LOW |
| **Doubling of serum creatinine or ESRD - Elderly (65 and older), 2 years follow-up** | | | | | | | | | | | |
| 1[7] | randomised trials | no serious risk of bias | no serious inconsistency[4] | serious[13] | Very serious[14] | none | 8/2212 (0.36%) | 9/2206 (0.41%) | RR 0.89 (0.34 to 2.29) | 0 fewer per 1000 (from 3 fewer to 5 more) | VERY LOW |
| **Doubling of serum creatinine or ESRD - Elderly (65 and older) with diabetes, 2 years follow-up** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency[4] | serious[13] | very serious[14] | none | 1/264 (0.38%) | 3/257 (1.2%) | RR 0.32 (0.03 to 3.1) | 8 fewer per 1000 (from 11 fewer to 25 more) | VERY LOW |
| **Progression to ESRD (follow-up 7 years)** | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 50/250 (20%) | 39/237 (16.5%) | RR 1.25 (0.85 to 1.82) | 41 more per 1000 (from 25 fewer to 135 more) | MODERATE |
| **Adverse events (all) (follow-up mean 5 years)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 508/5320 (9.5%) | 514/5264 (9.8%) | RR 0.98 (0.87 to 1.09) | 2 fewer per 1000 (from 13 fewer to 9 more) | HIGH |
| **Adverse events (all) (adults 80 years and older) (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 340/586 (58%) | 353/581 (60.8%) | HR 0.92 (0.79 to 1.07) | 30 fewer per 1000 (from 85 fewer to 25 more) | MODERATE |
| **Adverse events - Electrolyte abnormalities (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[2] | none | 69/1330 (5.2%) | 51/1316 (3.9%) | RR 1.34 (0.94 to 1.91) | 13 more per 1000 (from 2 fewer to 35 more) | MODERATE |
| **Adverse events - Electrolyte abnormalities (adults 80 years and older) (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 30/586 (5.1%) | 26/581 (4.5%) | RR 1.14 (0.69 to 1.91) | 6 more per 1000 (from 14 fewer to 41 more) | LOW |
| **Adverse events - Injurious fall (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[2] | none | 114/1330 (8.6%) | 138/1316 (10.5%) | RR 0.82 (0.65 to 1.04) | 19 fewer per 1000 (from 37 fewer to 4 more) | MODERATE |
| **Adverse events - Injurious fall (adults 80 years and older) (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[2,14] | none | 49/586 (8.4%) | 53/581 (9.1%) | RR 0.92 (0.63 to 1.33) | 7 fewer per 1000 (from 34 fewer to 30 more) | LOW |
| **Adverse events - Postural hypotension without dizziness (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 301/1330 (22.6%) | 302/1316 (22.9%) | RR 0.99 (0.86 to 1.13) | 2 fewer per 1000 (from 32 fewer to 30 more) | HIGH |
| **Adverse events - Postural hypotension with dizziness (follow-up mean 5 years)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 24/1330 (1.8%) | 23/1316 (1.7%) | RR 1.03 (0.59 to 1.82) | 1 more per 1000 (from 7 fewer to 14 more) | LOW |
| **Adverse events - Hypotension (adults 80 years and older) (follow-up mean 5 years)** | | | | | | | | | | | |
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[2] | none | 18/586 (3.1%) | 9/581 (1.5%) | RR 1.98 (0.9 to 4.38) | 15 more per 1000 (from 2 fewer to 52 more) | MODERATE |
| **Heart failure (all CKD) (follow-up median 3.2 years)** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 41/1330 (3.1%) | 52/1316 (4%) | RR 0.78 (0.52 to 1.17) | 9 fewer per 1000 (from 19 fewer to 7 more) | MODERATE |
| **Heart failure (CKD; UACR <30mg/g) (follow-up median 3.2 years)** | | | | | | | | | | | |
| 1[15] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 15/879 (1.7%) | 26/858 (3%) | RR 0.56 (0.30 to 1.16) | 13 fewer per 1000 (from 21 fewer to 5 more) | MODERATE |
| **Heart failure (CKD; UACR 30 to 300mg/g) (follow-up median 3.2 years)** | | | | | | | | | | | |
| 1[15] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[14] | none | 16/317 (5%) | 18/334 (5.4%) | RR 0.94 (0.49 to 1.80) | 3 fewer per 1000 (from 27 fewer to 43 more) | LOW |
| **Heart failure (CKD; UACR >300mg/g) (follow-up median 3.2 years)** | | | | | | | | | | | |
| 1[15] | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[14] | none | 9/136 (6.6%) | 8/126 (6.3%) | RR 1.04 (0.41 to 2.62) | 3 more per 1000 (from 37 fewer to 103 more) | LOW |
| **CVD morbidity (number of people) - Myocardial infarction** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 44/1330 (3.3%) | 45/1316 (3.4%) | RR 0.97 (0.64 to 1.46) | 1 fewer per 1000 (from 12 fewer to 16 more) | LOW |
| **CVD morbidity (number of people) - Acute coronary syndrome** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 15/1330 (1.1%) | 11/1316 (0.84%) | RR 1.35 (0.62 to 2.93) | 3 more per 1000 (from 3 fewer to 16 more) | LOW |
| **CVD morbidity (number of people) - Intracranial haemorrhage** | | | | | | | | | | | |
| 1[16] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 2/247 (0.81%) | 5/227 (2.2%) | RR 0.37 (0.07 to 1.88) | 14 fewer per 1000 (from 20 fewer to 19 more) | LOW |
| **CVD morbidity (number of people) - Stroke** | | | | | | | | | | | |
| 1[8] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 27/1330 (2%) | 27/1316 (2.1%) | RR 0.99 (0.58 to 1.68) | 0 fewer per 1000 (from 9 fewer to 14 more) | LOW |
| **CVD morbidity (number of people) - Recurrent stroke** | | | | | | | | | | | |
| 1[16] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 32/247 (13%) | 26/227 (11.5%) | RR 1.13 (0.7 to 1.84) | 15 more per 1000 (from 34 fewer to 96 more) | LOW |
| **CVD morbidity (number of people) - Coronary artery disease** | | | | | | | | | | | |
| 1[12] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 1/274 (0.36%) | 2/284 (0.7%) | RR 0.52 (0.05 to 5.68) | 3 fewer per 1000 (from 7 fewer to 33 more) | LOW |
| **CVD morbidity (number of people) - Arrhythmias** | | | | | | | | | | | |
| 1[12] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 1/274 (0.36%) | 4/284 (1.4%) | RR 0.26 (0.03 to 2.3) | 10 fewer per 1000 (from 14 fewer to 18 more) | LOW |
| **CVD morbidity (number of people) - Atrial fibrillation** | | | | | | | | | | | |
| 1[17] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | very serious[14] | none | 39/1123 (3.5%) | 38/1069 (3.6%) | RR 0.98 (0.63 to 1.52) | 1 fewer per 1000 (from 13 fewer to 18 more) | LOW |
| **CVD mortality (number of people) - Adults** | | | | | | | | | | | |

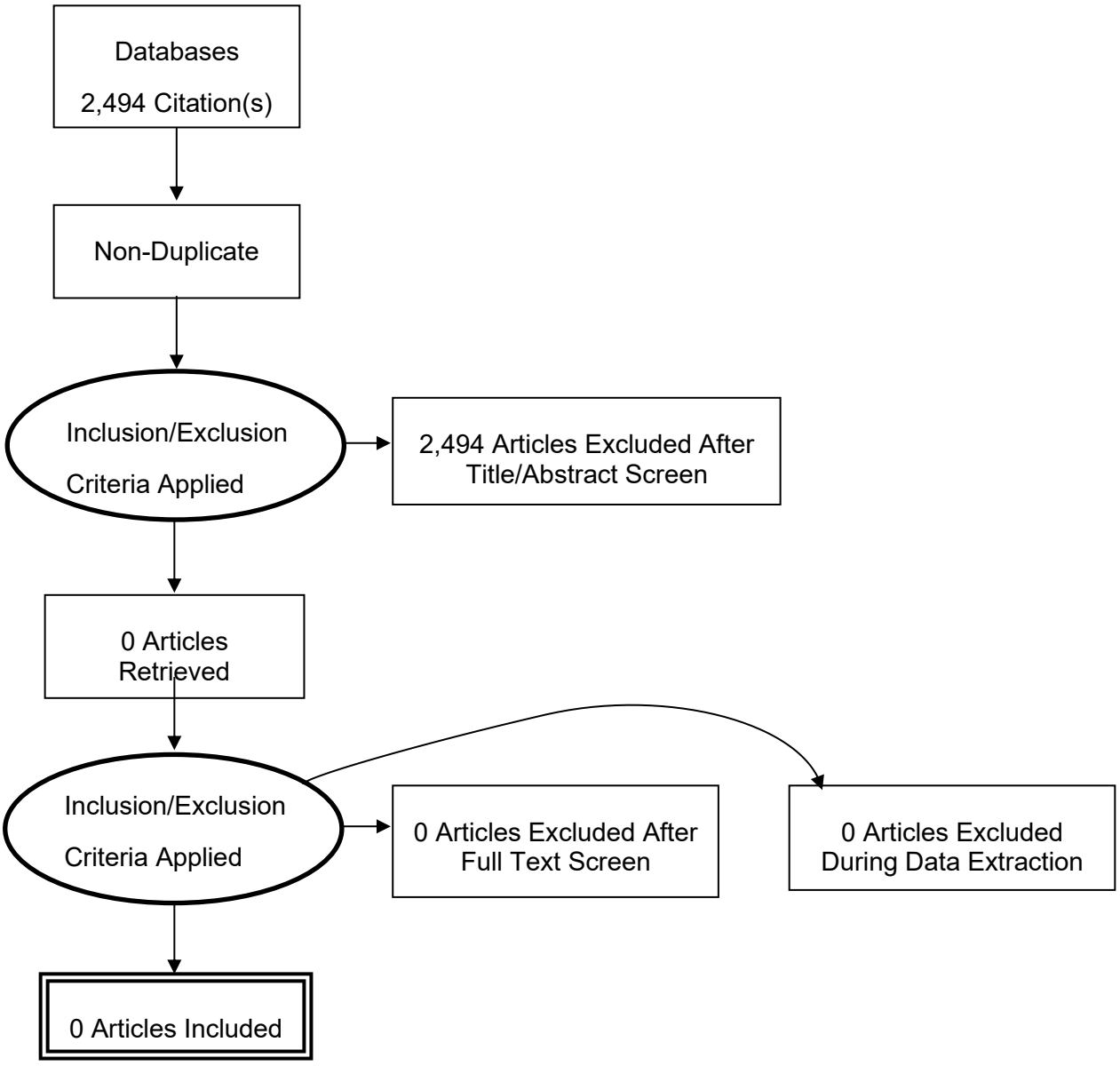
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[10] | none | 19/1497 (1.3%) | 32/1484 (2.2%) | RR 0.59 (0.33 to 1.03) | 9 fewer per 1000 (from 14 fewer to 1 more) | MODERATE |
| **All-cause mortality (number of people) - Adults** | | | | | | | | | | | |
| 6 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 105/2101 (5%) | 132/2064 (6.4%) | RR 0.77 (0.6 to 0.98) | 15 fewer per 1000 (from 1 fewer to 26 fewer) | HIGH |
| **All-cause mortality (number of people) - Children** | | | | | | | | | | | |
| 1[3] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 0/189 (0%) | 1/196 (0.51%) | RR 0.35 (0.01 to 8.43) | 3 fewer per 1000 (from 5 fewer to 38 more) | MODERATE |
| **All-cause mortality (number of people) - African American** | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 56/868 (6.5%) | 58/870 (6.7%) | RR 0.97 (0.68 to 1.39) | 2 fewer per 1000 (from 21 fewer to 26 more) | MODERATE |
| **All-cause mortality (number of people) - Older adults 80 years and over** | | | | | | | | | | | |
| 1[9] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | no serious imprecision | none | 69/586 (11.8%) | 92/581 (15.8%) | RR 0.74 (0.56 to 0.99) | 41 fewer per 1000 (from 2 fewer to 70 fewer) | HIGH |
| **Chronic heart failure (rate per year) in Type 2 diabetes - Any chronic heart failure (follow-up mean 3.5 years)** | | | | | | | | | | | |
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 12/867 (1.4%) | 13/859 (1.5%) | HR 0.92 (0.63 to 1.34) | 1 fewer per 1000 (from 6 fewer to 5 more) | MODERATE |
| **CVD morbidity (rate per year) in Type 2 diabetes - Non-fatal Myocardial Infarction (follow-up mean 3.5 years)** | | | | | | | | | | | |
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 15/867 (1.7%) | 16/859 (1.9%) | HR 0.89 (0.63 to 1.26) | 2 fewer per 1000 (from 7 fewer to 5 more) | MODERATE |
| **CVD morbidity (rate per year) in Type 2 diabetes - Non-fatal stroke (follow-up mean 3.5 years)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 4/867 (0.46%) | 6/859 (0.7%) | HR 0.64 (0.36 to 1.14) | 3 fewer per 1000 (from 4 fewer to 1 more) | MODERATE |
| **CVD morbidity (rate per year) in Type 2 diabetes - Any stroke (follow-up mean 3.5 years)** | | | | | | | | | | | |
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 4/867 (0.46%) | 7/859 (0.81%) | HR 0.62 (0.36 to 1.07) | 3 fewer per 1000 (from 5 fewer to 1 more) | MODERATE |
| **CVD mortality (rate per year) in Type 2 diabetes (follow-up mean 3.5 years)** | | | | | | | | | | | |
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 7/867 (0.81%) | 7/859 (0.81%) | HR 0.93 (0.57 to 1.52) | 1 fewer per 1000 (from 3 fewer to 4 more) | MODERATE |
| **All cause mortality (rate per year) in Type 2 diabetes (follow-up mean 3.5 years)** | | | | | | | | | | | |
| 1[18] | randomised trials | no serious risk of bias | no serious inconsistency[4] | no serious indirectness | serious[10] | none | 16/867 (1.8%) | 15/859 (1.7%) | HR 0.86 (0.63 to 1.17) | 2 fewer per 1000 (from 6 fewer to 3 more) | MODERATE |

[1] Downgraded two levels as I squared statistic > 66.7% despite using random effects model (see methods appendix B for details)
[2] Downgraded 1 level as 95% CI crossed one MID (mean difference of 0.5 x SD in control arm or MIDs of 0.8 and 1.25 in relative risks).
[3] ESCAPE 2004
[4] Not applicable.
[5] AASK 2002
[6] MDRD 1994
[7] JATOS 2010
[8] SPRINT 2017
[9] SPRINT (aged 80 years and older; Pajewski 2020)
[10] Downgraded one level as 95% CI crosses line of no effect for hazard ratios or mortality outcomes.
[11] Toto 1995
[12] Schrier 2014
[13] Indirect measure for progression to ESRD or ESKD.
[14] Downgraded 2 levels as 95% CIs crosses 2 MIDs (both 0.8 and 1.25 in relative risks).
[15] SPRINT (reported by Vaduganathan 2020)
[16] SPS3 2019

[17] SPRINT (reported by Soliman 2020)
[18] ACCORD 2016

# Appendix H – Economic evidence study selection



# Appendix I – Economic evidence tables

No economic evidence was included in this review.

# Appendix J – Health economic model

No health economic modelling was undertaken for this review.

# Appendix K – Excluded studies

| Study | Reason for exclusion |
|---|---|
| Appel, LJ, Wright, JT, Greene, T et al. (2010) Intensive blood-pressure control in hypertensive chronic kidney disease. New England journal of medicine 363(10): 918-929 | - Post-hoc analysis which does not provide additional data of relevance to this review.<br>[no outcomes of relevance to this review are presented for the trial phase of the study; the cohort phase of the study was not included for this review as it is not an RCT] |
| Arguedas, Jose Agustin; Leiva, Viriam; Wright, James M (2013) Blood pressure targets for hypertension in people with diabetes mellitus. The Cochrane database of systematic reviews: cd008277 | - Systematic review used as a source of primary studies |
| Aydin, V., Akici, A., Sakarya, S. et al. (2020) Baseline characteristics predicting clinical outcomes and serious adverse events in middle-aged hypertensive women: A subanalysis of the sprint in women aged <65 years. Turkish Journal of Medical Sciences 50(5): 1298-1306 | - Post-hoc analysis which does not provide additional data of relevance to this review<br>[CKD compared no CKD] |
| Bavishi, Chirag; Bangalore, Sripal; Messerli, Franz H (2017) Outcomes of Intensive Blood Pressure Lowering in Older Hypertensive Patients. Journal of the American College of Cardiology 69(5): 486-493 | - Systematic review used as a source of primary studies |
| Beddhu, Srinivasan, Greene, Tom, Boucher, Robert et al. (2018) Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. The lancet. Diabetes & endocrinology 6(7): 555-563 | - population does not match protocol<br>[participants did not have CKD] |
| Bhavsar, Nrupen A, Appel, Lawrence J, Kusek, John W et al. (2011) Comparison of measured GFR, serum creatinine, cystatin C, and beta-trace protein to predict ESRD in African Americans with hypertensive CKD. American journal of kidney diseases : the official journal of the National Kidney Foundation 58(6): 886-93 | - Post-hoc analysis which does not provide additional data of relevance to this review. |
| Carter, Barry L, Coffey, Christopher S, Ardery, Gail et al. (2015) Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. Circulation. Cardiovascular quality and outcomes 8(3): 235-43 | - Intervention does not match protocol<br>[did not assign target BPs] |
| Collard, D., Brouwer, T.F., Olde Engberink, R.H.G. et al. (2020) Initial estimated glomerular filtration rate decline and long-term renal function during intensive antihypertensive therapy a post hoc analysis of the SPRINT and ACCORD-BP randomized controlled trials. Hypertension: 1205-1212 | - Post-hoc analysis which does not provide additional data of relevance to this review.<br>[This post hoc analysis included participants with and without CKD] |
| D'Anci, K.E., Tipton, K., Hedden-Gross, A. et al. (2020) Effect of Intensive Blood Pressure Lowering on Cardiovascular Outcomes: A Systematic Review Prepared for the 2020 U.S. Department of Veterans Affairs/U.S. Department | - Systematic review used as source of systematic reviews |

| Study | Reason for exclusion |
|---|---|
| of Defense Guidelines. Annals of internal medicine | |
| Futier, E., Lefrant, J.-Y., Guinot, P.-G. et al. (2017) Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction 6among high-risk patients undergoing major surgery: A randomized clinical trial. JAMA - Journal of the American Medical Association 318(14): 1346-1357 | - population does not match protocol [Participants with CKD were excluded] |
| Ismail-Beigi, Faramarz, Craven, Timothy E, O'Connor, Patrick J et al. (2012) Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. Kidney international 81(6): 586-94 | - Post-hoc analysis which does not provide additional data of relevance to this review. |
| Kitzman, DW, Oparil, S, Lewis, CE et al. (2016) Intensive blood pressure treatment consistently reduces heart failure events across all key subgroups in the sprint study. Journal of the american society of hypertension 10(4): e3-e4 | - Conference abstract |
| Ku, Elaine, Glidden, David V, Johansen, Kirsten L et al. (2015) Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. Kidney international 87(5): 1055-60 | - Post-hoc analysis which does not provide additional data of relevance to this review. |
| Ku, Elaine, Ix, Joachim H, Jamerson, Kenneth et al. (2018) Acute Declines in Renal Function during Intensive BP Lowering and Long-Term Risk of Death. Journal of the American Society of Nephrology : JASN 29(9): 2401-2408 | - Post-hoc analysis which does not provide additional data of relevance to this review. |
| Ku, Elaine, McCulloch, Charles E, Mauer, Michael et al. (2016) Association Between Blood Pressure and Adverse Renal Events in Type 1 Diabetes. Diabetes care 39(12): 2218-2224 | - population does not match protocol [participants did not have CKD] |
| Lewis, J B, Berl, T, Bain, R P et al. (1999) Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. American journal of kidney diseases : the official journal of the National Kidney Foundation 34(5): 809-17 | - population does not match protocol [participants were not required to have CKD.] |
| Li, L. (2019) Intensive versus usual control of hypertension in the prevention of cardiovascular and renal outcomes: A cumulative meta-analysis of randomized controlled trials. Kidney and Blood Pressure Research 44(3): 384-395 | - Systematic review used as a source of primary studies |
| Malhotra, Rakesh, Nguyen, Hoang Anh, Benavente, Oscar et al. (2017) Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5: A Systematic Review and Meta-analysis. JAMA internal medicine 177(10): 1498-1505 | - Systematic review used as a source of primary studies |

| Study | Reason for exclusion |
|---|---|
| Matteucci, Maria Chiara, Chinali, Marcello, Rinelli, Gabriele et al. (2013) Change in cardiac geometry and function in CKD children during strict BP control: a randomized study. Clinical journal of the American Society of Nephrology : CJASN 8(2): 203-10 | - Post-hoc analysis which does not provide additional data of relevance to this review. |
| Mottl, Amy K, Buse, John B, Ismail-Beigi, Faramarz et al. (2018) Long-Term Effects of Intensive Glycemic and Blood Pressure Control and Fenofibrate Use on Kidney Outcomes. Clinical journal of the American Society of Nephrology : CJASN 13(11): 1693-1702 | - Post-hoc analysis which does not provide additional data of relevance to this review<br>[This post hoc analysis included participants with and without CKD] |
| Murad, M.H., Larrea-Mantilla, L., Haddad, A. et al. (2019) Antihypertensive Agents in Older Adults: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. The Journal of clinical endocrinology and metabolism 104(5): 1575-1584 | - Systematic review used as a source of primary studies |
| NCT03585595 (2018) Intensive Blood Pressure Intervention in Stroke (IBIS) Trial. https://clinicaltrials.gov/show/NCT03585595 | - on-going clinical trial |
| Palmer, Suetonia C, Maggo, Jasjot K, Campbell, Katrina L et al. (2017) Dietary interventions for adults with chronic kidney disease. The Cochrane database of systematic reviews 4: cd011998 | - Systematic review used as a source of primary studies |
| Rayamajhi, S, Wang, L, Dhaka, P et al. (2018) Hypertension and kidney disease: effect of intensive blood pressure intervention. Journal of hypertension 36: e289 | - Conference abstract |
| Rostomian, A.H., Tang, M.C., Soverow, J. et al. (2020) Heterogeneity of treatment effect in SPRINT by age and baseline comorbidities: The greatest impact of intensive blood pressure treatment is observed among younger patients without CKD or CVD and in older patients with CKD or CVD. Journal of Clinical Hypertension | - Post-hoc analysis which does not provide additional data of relevance to this review<br>[Data reported only for composite outcome] |
| Tsai, Wan-Chuan, Wu, Hon-Yen, Peng, Yu-Sen et al. (2017) Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. JAMA internal medicine 177(6): 792-799 | - Systematic review used as a source of primary studies |
| Upadhyay, Ashish, Earley, Amy, Haynes, Shana M et al. (2011) Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Annals of internal medicine 154(8): 541-8 | - Systematic review used as a source of primary studies |
| Wu, X., Jiang, Z., Ying, J. et al. (2017) Optimal blood pressure decreases acute kidney injury after gastrointestinal surgery in elderly hypertensive patients: A randomized study: Optimal blood pressure reduces acute kidney injury. Journal of Clinical Anesthesia 43: 77-83 | - population does not match protocol<br>[Data were not available for participants with CKD] |

| Study | Reason for exclusion |
|---|---|
| Xie, Xinfang, Atkins, Emily, Lv, Jicheng et al. (2016) Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet (London, England) 387(10017): 435-43 | - Systematic review used as a source of primary studies |
| Zhang, William R, Craven, Timothy E, Malhotra, Rakesh et al. (2018) Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction: A Case-Control Study. Annals of internal medicine 169(9): 610-618 | - Study design does not match protocol [Nested case–control study within SPRINT.] |

# Appendix L – Additional evidence

**Table 7: Evidence relating to proteinuria and composite outcomes**

| Study | Result reported |
|---|---|
| AASK (African American) | • There were no significant interactions noted between BP goal assignment and proteinuria, baseline GFR, or antihypertensive drug assignment (all P.0.05) for the outcome of mortality.<br>• There was a statistically significant interaction between BP assignment and proteinuria for the risk of ESRD (P=0.02).<br>• For participants who had < 1 g/d proteinuria at baseline (n=892), risk of ESRD was 1.05 (95% CI, 0.83 to 1.32) comparing strict versus usual BP arms.<br>• In participants who had > 1 g/d proteinuria at baseline (n=175), risk of ESRD was 0.59 (95% CI, 0.41 to 0.85) comparing strict versus usual BP arms in unadjusted analysis.<br>• Table 72 in CG182 reports that intensive BP control reduces proteinuria risk, although this was not reported in Ku 2017. |
| ACCORD | • Composite end point: non-fatal and fatal CVD events (first occurrence of non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death) = 0.86 (0.67, 1.11) |
| ESCAPE (children) | • the change in 24-hour MAPSDS was positively correlated with the degree of proteinuria (r = 0.25; P < 0.0001)<br>• The antihypertensive response was significantly greater in patients with gross proteinuria (urinary protein/creatinine ratio>1) (change in MAP −1.8 ± 1.8 SDS) than in children with mild or no proteinuria (−1.0±1.4 SDS; P<0.0005).<br>• Multivariate regression: positively associated with reduction in 24hr MAP SDS - baseline proteinuria (positive effect, partial r2 = 0.017, P < 0.01).<br>• Composite outcome: 50% reduction in the glomerular filtration rate or progression to end-stage renal disease (glomerular filtration rate <10 ml per minute per 1.73 $m^2$ or start of renal-replacement therapy).<br>○ HR: 0.65 (95% confidence interval [CI], 0.44 to 0.94; P=0.02).<br>○ Higher proteinuria associated with increased overall risk of reaching primary end point |
| JATOS (elderly) | • In subjects with proteinuria, eGFR remained unaltered during the trial period (P = 0.3431).<br>• In patients in whom proteinuria disappeared during the trial period, proteinuria was elevated.<br>• Proteinuria at the time of entry into the trial constituted a strong risk predictor of cardiovascular events (P=0.0001), particularly in patients with baseline eGFR < 60 ml/min. |
| MDRD<br>(Peterson 1995 – proteinuria post-hoc analysis) | • MAP in the usual blood pressure group increased from 99.6 mm Hg at baseline to 100.1 mm Hg during follow-up in patients with baseline proteinuria of 1.0 g/d or more<br>• MAP increased from 95.2 mm Hg at baseline to 96.5 mm Hg during follow-up in patients with baseline proteinuria of less than 1.0 g/d.<br>• In low BP group, MAP declined during follow-up in patients with baseline proteinuria of 1.0 g/d or more<br>• MAP declined from 95.4 mm Hg at baseline to 92.5 mm Hg during follow-up in patients with baseline proteinuria of less than 1.0 g/d. |

| Study | Result reported |
|---|---|
| | • In patients with baseline proteinuria of 3 or more, a greater decline in glomerular filtration rate was seen at mean arterial pressures greater than about 92 mm Hg.<br>• Low blood pressure goal can delay the increase in proteinuria, even in patients with low baseline proteinuria. |
| REIN-2 | • Patients with proteinuria 3g or more: HR of progression to ESRD: 1.09 ( 0.55– 2.19), baseline < 3g also not significant<br>• Proteinuria (and serum creatine) significantly predicted rate of GFR decline. |
| SPRINT | • Excluded proteinuria > 1 g/d<br>• Composite CV outcome of 50% or more decrease in eGFR from baseline or ESRD = HR, 0.90; 95% CI, 0.44 to 1.83.<br>• Composite CV outcome (nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes) in people aged 80 years and older: HR 0.67 (95% CI 0.50 to 0.90) |
| SPS3 | • None |
| Schrier 2002 | • None |
| Schrier 2014 | • None |
| Toto 1995 | • There was a significant negative correlation between GFR slope and baseline proteinuria in patients with baseline protein excretion > 500 mg/day (r = 0.53, P < 0.03). |