National Clinical Guideline Centre

NICE clinical guideline CG181

Lipid modification

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Clinical Guideline

Appendices

July 2014

Final version

Commissioned by the National Institute for Health and Care Excellence

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Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

1.1 Short title

Lipid modification

2 The remit

This is a partial update of:

- Lipid modification (NICE clinical guideline 67, 2008)
- Statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94, 2006).

See section 4.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

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

3 Clinical need for the guideline

3.1 Epidemiology

a) Cardiovascular disease (CVD) is defined for epidemiological and trial purposes as fatal and non-fatal coronary heart disease, stroke and peripheral arterial disease that need intervention.

b) CVD is 1 of a number of diseases associated with atherosclerosis (hardening and narrowing of the arteries). Other diseases

associated with atherosclerosis include aortic aneurysm, acute onset heart failure after myocardial infarction, chronic heart failure, and cardiac arrhythmias. Although they share common risk factors, their disease processes and management differ.

c) CVD has significant cost implications.

d) CVD is a major cause of morbidity in England, with a prevalence of 13.6% in men and 13.0% in women.

e) CVD is the leading cause of death in the UK. In 2008 diseases of the circulatory system caused 190,857deaths in the UK, of which 88,236 were due to coronary heart disease and 43,142 to stroke. The death rate varies with age, gender, socioeconomic status, ethnicity and geographic location. Death rates for CVD have been falling in the UK since the 1970s. About 58% of this decline during the 1980s and 1990s is attributable to reductions in major risk factors, principally smoking. Treatment of people at risk, including secondary prevention, accounts for the remaining 42%.

3.2 Current practice

a) Strategies for the primary prevention of CVD have focused on interventions to reduce risk factors for CVD and on identifying, assessing and treating people who are at high risk of developing CVD but currently have no symptoms. The risk assessment stage of the NHS Health Check (formerly known as the Vascular Check Programme) uses a risk engine for people aged 40–74 years to calculate their 10-year risk of CVD. In both primary and secondary prevention, the focus is on dealing with modifiable risk factors such as smoking, high blood pressure, blood lipids, physical inactivity and obesity.

b) Blood lipids, including cholesterol, are a modifiable risk factor for CVD. The risk of CVD is directly related to blood cholesterol levels and it is estimated that more than 50% of CVD in developed

countries is a result of blood cholesterol levels higher than 3.8 mmol/litre. Blood cholesterol and other lipid components can be modified by drugs, physical activity and dietary changes; a multifactorial approach is likely to yield most benefit.

c) Drug therapy, although important, must be seen in the context of other interventions to reduce absolute risk of CVD. The use of lipid-lowering drugs in primary and secondary prevention has major cost implications. The net ingredient cost of lipid-lowering drugs dispensed in the community in 2011 was £544,187,400.

4 The guideline

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

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

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

4.1 Population

4.1.1 Groups that will be covered

a) Adults (aged 18 years and older) without established CVD.

b) Adults with type 1 diabetes (not covered in the original guideline).

c) Adults with type 2 diabetes (not covered in the original guideline).

d) Adults with chronic kidney disease (CKD) (not covered in the original guideline).

e) Adults (aged 18 and older) with established CVD.

f) The following special groups will be considered:

- people from black and minority ethnic groups
- people with a family history of CVD
- people from low socioeconomic groups
- people older than 75
- women
- people with autoimmune disease
- people with serious mental illness.

4.1.2 Groups that will not be covered

a) People with familial hypercholesterolaemia.

b) People with familial clotting disorders that increase cardiovascular risk.

c) People with other genetic disorders that increase cardiovascular risk.

d) People at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes other than diabetes.

e) People receiving renal replacement therapy.

4.2 Healthcare setting

a) All settings in which NHS care is delivered.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) The most appropriate risk tool system to estimate a person's absolute risk of developing CVD for:

- people without diabetes – for example, age alone, QRISK and Framingham risk assessment tools (10-year or lifetime risk)

- people with diabetes – for example, age alone, QRISK and UKPDS Risk Engine tools (not covered in the original guideline).

b) Lipid modification strategy: for example, fixed dose or treating to a target lipid level.

c) Pharmacological interventions (1) to reduce the risk of developing CVD (primary prevention) and (2) for secondary prevention in people with established CVD:

- First-line treatment:
  - statins.
- Second-line treatment (alone or in combination with statins):
  - fibrates
  - anion-exchange resins
  - nicotinic acid group
  - omega-3 fatty acids.

d) Cardioprotective diet, including plant stanols and sterols.

e) Assessment of blood lipids: which fractions of blood lipids should be measured and in what circumstances (for example, fasting).

f) Identifying subgroups at increased risk of adverse events, and strategies to maintain and improve adherence to individual agents, for example coenzyme Q_{10}.

g) Monitoring lipid-lowering treatment, for example, blood lipids, liver function test, creatine kinase and glycaemia.

h) Criteria for referral to specialist assessment and management for people found to have lipid disorders, for example familial lipid disorders.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will

assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

4.3.2 Clinical issues that will not be covered

a) Identifying and assessing prediabetes or metabolic syndrome, and their management beyond the lipid abnormalities present in this condition.

b) The identification and management of people with Type 1 diabetes, Type 2 diabetes and Chronic Kidney Disease other than in relation to risk assessment for cardiovascular disease and lipid modification.

c) Assessment and clinical management of modifiable risk factors for cardiovascular disease other than lipid modification such as raised blood pressure or hypertension, smoking, obesity and blood clotting abnormalities.

d) Self-medication with lipid-regulating drugs, specifically over-the-counter drugs, including statins.

e) Clinical management of lipid disorders considered to merit referral to secondary care for specialist assessment and follow-up.

f) Secondary prevention of myocardial infarction other than lipid modification.

4.4 Main outcomes

a) Morbidity and mortality.

b) Hospitalisation.

c) 10-year risk of developing CVD.

d) Lifetime risk of developing CVD.

e) Adverse events.

f) Quality of life outcomes.

g) Adherence.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

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

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- Lipid modification. NICE clinical guideline 67 (2008).
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006).

5.1.2 Other related NICE guidance

- Hypertension. NICE clinical guideline 127 (2011)

- Type 2 diabetes – newer agents. NICE clinical guideline 87 (2009)
- Medicines adherence. NICE clinical guideline 76 (2009)
- Familial hypercholesterolaemia. NICE clinical guideline 71 (2008)
- Stroke. NICE clinical guideline 68 (2008)
- MI: secondary prevention. NICE clinical guideline 48 (2007)
- Prevention of cardiovascular disease at the population level. NICE public health guidance 25 (2011)
- Identifying and supporting people most at risk of dying prematurely. NICE public health guidance 15 (2008)
- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. NICE technology appraisal guidance 210 (2010)
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007).

5.2 Guidance under development

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

- Lower limb peripheral arterial disease. NICE clinical guideline. Publication expected August 2012.
- Preventing type 2 diabetes – risk identification and interventions for individuals at high risk. NICE public health guidance. Publication expected June 2012.
- Myocardial infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline. Publication expected July 2013.
- Myocardial infarction with ST-segment-elevation. NICE clinical guideline. Publication expected July 2013.
- Chronic kidney disease. NICE clinical guideline. Publication expected July 2014.
- Type 1 diabetes: the diagnosis and management of type 1diabetes in adults (update). NICE clinical guideline. Publication expected July 2014

- Type 2 diabetes. NICE clinical guideline. Publication expected TBC.

6 Further information

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

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

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

Appendix B: Declarations of interest

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process.

B.1 Full GDG members

Dr Anthony Wierzbicki (Chair)

GDG meeting	Declaration of Interests	Action taken
Chair recruitment	None.	None
First GDG meeting (11 September 2012)	Non-personal pecuniary interest: Clinical trials (FH) – HPS2 – THRIVE (BHF/HSD) (Sanofi – Aventis, Amgen, Pfizer), Mipomersen (Genzyme), Ezetimibe (MSD). Personal non-pecuniary interest: Editorials on topics of cardiovascular disease and Lipids. Academic publications.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	Personal non-pecuniary interest: Publications on CVD risk assessment 2003-2008. Member, London SE & SW Cardiac Network Groups (NHS checks) 2008-13.	None
Eight GDG Meeting (11 September 2013)	Personal non-pecuniary interest: Clinical Lead: Blood Sciences (including clinical biochemistry) Laboratories GSTS Pathology (2010–now) Site investigator: Clinical trial of Amgen AMG-145 in familial hypercholesterolaemia (2013) Site investigator: Clinical trial of anacetrapib in patients with cardiovascular disease (HPS3/REVEAL) (2012–2017) Site investigator: Clinical outcomes trial of AMG-145 in patients at high cardiovascular risk (to start 2013)	None
Ninth GDG	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Meeting (12 September 2013)		
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	Personal non-pecuniary interest: Lead UK investigator: Pfizer RN-316 (anti-PCSK9 antibody; LDL-C reduction) programme Site investigator AMG-145 (anti-PCSK9 antibody)- Osler lipids follow-on study; Fourier CVD outcomes study.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record.	None

Dr Rajai Ahmad

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No declaration of interest	None
First GDG meeting (11 September 2012)	Personal pecuniary interest: Received speaker fees from Bayer and Boehringer Ingelheim for providing educational presentations and from Bayer for participation in advisory board during 2012. Scheduled to participate on (MSD) symposium on commissioning in CVD (out 2012) prevention peri-med.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
2013)		
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	No changes to record.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Ms Lindsay Banks

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	Personal non-pecuniary interest: Editor, NICE bites – independent bulletin.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	No changes to record.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Ms Liz Clark

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	No changes to record.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None
Ninth GDG	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Meeting (12 September 2013)		
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	Personal non pecuniary interest: has been involved in some NICE guidelines and activities: Chest Pain; Stable Angina quality Standard; Hypertension quality Standard; Diagnostic Advisory Committee - Cardiac Biomarkers.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Dr Martin Duerden

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	Personal non-pecuniary: Have written a number of articles and editorials on subject of Lipid modification. (None for several years).	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2013)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None
Ninth GDG Meeting	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
(12 September 2013)		
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	Persona non-pecuniary interest: I have been asked to review the North Wales Lipid lowering guideline.	None
Twelfth GDG Meeting (04 April 2014)	I gave talks on the 23rd January and the 10th February 2014 at meetings organised by Reckitt-Benckiser on the subject of antimicrobial stewardship. I received payment for this work.	None

Mrs Eleanor Grey

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	No changes to record.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None
Ninth GDG Meeting (12 September	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
2013)		
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	No changes to record.	None

Dr Michael Khan

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	Personal pecuniary interest: Advisory board 3 months ago – Genzyme on high risk FH. 2 half day meetings. Non-specific fee paid on Mipomersen. Advisory board for Amgen on PCSK9 monoclonal and B. Non-personal pecuniary interest: Previous support for FH cascade nurse (AZ + Pfizer) specialist for 12 months. Now supported by the trust with no industry contribution. Lecture to Lipid nurses on FH at Astra Zenara next week. Clinical trial of PCSK9 MAB – Amgen starting 2013.	None
Second GDG Meeting (24 October 2012)	Personal pecuniary interest: Non-executive director silence therapeutics (AIM listel). Only RNA in oncology – no CVD interest or conflicting funding. Advisory board for Amgen on PCSK9 mAb.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	Personal pecuniary interest: Part time salaried position as Chief Medical Officer of Silence Therapeutics. This is an RNAi therapy development company. Non-personal pecuniary interest: Clinical trial of a new monoclonal antibody directed at PCSK9 to be run at UHCW later this year. Personal non-pecuniary interest: Chair and Director of the Warwick University Masters Program in Cardiovascular Risk.	None
Fifth GDG Meeting (15 March 2013)	Personal pecuniary interest: I gave a talk at Expo on FH; this was sponsored by an educational grant to the Organising committee by AstraZeneca.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG	Personal non-pecuniary interest:	None

GDG meeting	Declaration of Interests	Action taken
Meeting (31 May 2013)	Involved in developing several local guidelines in Warwickshire. Published a long time ago on risk of CVD. Currently involved discussion, on behalf of the Midlands, with various organisations, including central government and Heart UK about FH. Involved in risk calculations in cancer.	
Eight GDG Meeting (11 September 2013)	Personal pecuniary interest: CMO and Director of Silence Therapeutics Ltd. This is an RNAi therapeutics development company, which has an oncology drug (siRNA against PKN3) in clinical trials in pancreatic cancer. There are no lipid-related drugs in clinical development yet, but the company are interested in preclinical studies of novel targets for homozygous FH, including ApoB, which has no connection to this panel. I have shares in and am a director (unpaid) of Pharmalogos Ltd (owned by my wife), which provides bioinformatics support and histology services in cancer biology and also produces educational materials in cancer biology. They have provided educational/training activity in FH (not related to this CDDG) on behalf of Astra-Zeneca. There is no link to any other lipid or CVD related area at this point, but the company may provide consultancy/advisory services in these areas in the future. I have sat on paid advisory boards (Genzyme/Sanofi) for FH and severe hypertriglyceridaemia (Novartis).These are not related to this CGDG. Personal family interest: My wife is a director of Pharmalogos Ltd (see above). Non-personal pecuniary interest: Course Director of the Warwick masters and PGA in Cardiovascular Risk. This course hasn't run during the period of activity of this CGDG. When it does there is no particular viewpoint promoted the course lectures simply provide a presentation of the national guidelines from NICE and other relevant bodies as they stand at the time. Personal non-pecuniary interest: I am running a clinical trial of a PCSK9 monoclonal antibody (Amgen) in FH. Astra-Zeneca and Pfizer have provided financial support to my Trust (UHCW) to help establish our FH cascade screening programme. This is part of a joint-working agreement between Astra-Zeneca and UHCW. I have no personal financial interest and the remit is solely around FH, which is not related to this CGDG	None
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November	Personal pecuniary interest: Increased role as CMO of Silence Therapeutics to 4 days a week. No lipid or CVD interest at this time.	None

GDG meeting	Declaration of Interests	Action taken
2013)	Advisory board Novartis: DGAT1 inhibitor in trials. Personal family interest: Advisor to Oxford Pharmascience on one occasion on behalf of my wife's company. No drugs on the market yet. Personal non-pecuniary interest: Production of an educational video on FH. Will be host and local organiser of Heart UK 2014.	
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Mrs Emma McGowan

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	Non-personal pecuniary interest - My post was originally sponsored by a Pharmaceutical Company for 1 year. This was from November 2010 until November 2011. Since then I have been employed by UHCW NHS Trust.	None
First GDG meeting (11 September 2012)	Personal pecuniary interest: I received personal payment from Merck Sharp Dohm 27/02/2012 for speaking at a meeting for nurses. It was non promotional discussing the nurse led service for Familiar Hypercholesterolemia (FH). I received personal payment from Astra Zeneca UK 19/04/2012 to enable me to attend the Heart UK Annual conference. The payments were made personally as I have been informed they are unable to pay into a departmental fund. All of the personal payments I have received have been used to pay for meetings and conferences I have attended as I do not receive any funding for these events from my employer. Non-personal pecuniary interest: My post was originally sponsored by a Pharmaceutical Company for 1 year. This was from November 2010 until November 2011. Since then I have been employed by UHCW NHS Trust. As previously discussed, my post was originally sponsored by the Pharmaceutical company Astra Zeneca for the first 12 months. It has now been adopted by UHCW NHS trust. The FH services have been in discussion with Astra Zeneca with reference to a working partnership and provision of nurse support. My post was originally sponsored by Astra for 12 months. The FH service is in discussion with Amgen in Relation to conducting a clinical trial in 2013.	None
Second GDG Meeting (24 October 2012)	Personal non-pecuniary interest: Participated in an education session for G.Ps on FH.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	Non-personal pecuniary interest: I am participating as a research nurse in an AMGEN Clinical trial. It includes a FH cohort of patients involving an injectable PCSK9 inhibitor	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	Non-personal pecuniary interest: I am currently study coordinator for an Amgen study. This is looking at a PCSK9 inhibitor for patients with Familial Hypercholesterolaemia (FH)	None
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	Personal non-pecuniary interest: I have recently been involved in the making of a video on Familial Hypercolesterolaemia (FH). This was made by ITN on behalf of Astrazeneca and Heart UK. It was non-commercial focusing on the provision of our FH service in Coventry and the importance of cascade screening. It will be used for the NHS alliance aimed at commissioners.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Dr Robert Dermot Neely

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	Personal pecuniary interest: In the past 12 months I have participated in one-off advisory boards for pharmaceutical companies developing lipids modifying therapy for specialist use in poorly treatment responsive and/or severe inherited lipids disorders, including Roche Pharma (dalcetrapib), Genzyme (mipomersen), and Aegerion (lomitapide). However I have no ongoing contractual relationships with any pharmaceutical companies and do not intend to undertake any further advisory work during in the period relevant to participation in the GDG, if offered a position.	None

GDG meeting	Declaration of Interests	Action taken
	Non-personal pecuniary interest: Newcastle upon Tyne hospital NHS foundation trust/Newcastle university clinical research facility participates in commercial clinical trials including those of novel lipid lowering therapy for Familial Hypercholesterolemia, for which I have had responsibility for recruiting some of the eligible patients. Personal non-pecuniary interest: I am a Trustee and board member of the Heart UK the Cholesterol Charity and Co-Chairman of the Familiar Hypercholesterolemia Guideline implementation group, a multi-disciplinary team which since 2008 has campaigned for the full implementation in England of the NICE Clinical Guideline CG71 and has developed and published a Guideline implementation toolkit on the Heart UK web site. I have participated and I am a member of Newcastle FATS guideline group on cholesterol lowering treatment.	
First GDG meeting (11 September 2012)	Personal pecuniary interest - Sponsorship to attend European Arteriosclerosis society (May 2012 - Merck). Personal non-pecuniary interest - I have participated and am a member of Newcastle FATS guideline group on cholesterol lowering treatment.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	Personal pecuniary interest: In 2011–2012 I participated in one-off Advisory Boards for pharmaceutical companies developing lipid modifying therapy for specialist use in poorly treatment responsive and/or severe inherited lipid disorders, including Roche Pharma (dalcetrapib), Genzyme (mipomersen), and Aegerion (lomitapide). I have been invited by Sanofi UK & Ireland to participate in the UK Lipid Strategic Advisory Board to be held on Friday 12th April 2013, regarding a new product in development for treatment of hypercholesterolaemia, for which I will receive an honorarium. Non-personal pecuniary interest: Newcastle upon Tyne Hospitals NHS Foundation Trust / Newcastle University Clinical Research Facility participates in commercial clinical trials including those of novel lipid lowering therapy for Familial Hypercholesterolaemia, for which I have had responsibility for recruiting some of the eligible patients. Personal non-pecuniary interest: I am a Trustee and Board member of HEART UK the Cholesterol Charity and Co-Chairman of the Familial Hypercholesterolaemia Guideline Implementation Group, a multi-disciplinary team which	None

GDG meeting	Declaration of Interests	Action taken
	since 2008 has campaigned for the full implementation in England of the NICE Clinical Guideline CG71 and has developed and published a Guideline Implementation Toolkit on the HEART UK Web site.	
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	Personal pecuniary interest: I have been invited by Sanofi UK & Ireland to participate in the UK Lipid Strategic Advisory Board to be held on Friday 12th April 2013, regarding a new product in development for treatment of hypercholesterolaemia, for which I will receive an honorarium. Non-personal pecuniary interest: Newcastle upon Tyne Hospitals NHS Foundation Trust / Newcastle University Clinical Research Facility participates in commercial clinical trials including those of novel lipid lowering therapy for Familial Hypercholesterolaemia, for which I have had responsibility for recruiting some of the eligible patients. Personal non-pecuniary interest: I am a Trustee and Board member of HEART UK the Cholesterol Charity and Co-Chairman of the Familial Hypercholesterolaemia Guideline Implementation Group, a multi-disciplinary team which since 2008 has campaigned for the full implementation in England of the NICE Clinical Guideline CG71 and has developed and published a Guideline Implementation Toolkit on the HEART UK Web site. Since 2002 I have been a member of the FATS Guideline Group, Newcastle and Northumberland which produces local guidance for primary and secondary care cardiovascular risk assessment and lipid management. The most recent version (FATS6) was published on the North East SHA web site. This work is non-remunerated. I have recently given an educational lecture on emerging therapies for Familial Hypercholesterolaemia at the HEART UK North West Lipid Forum, Manchester, 11 June 2013. The meeting was supported by Sanofi UK & Ireland but I was not remunerated for my participation.	None
Eight GDG Meeting (11 September 2013)	Non-personal pecuniary interest: I am employed by Newcastle upon Tyne Hospitals NHS Foundation Trust as a Consultant and Clinical Lead for Clinical Biochemistry Department, a contracted provider of lipid profiles and other blood tests to primary and secondary care organisations which generate income for the Trust. I am also Clinical Lead for the Lipid and Metabolic Clinic in the same Trust, which accepts patient referrals for investigation and management of lipid disorders, which generate income for the Trust.	None
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG	Personal pecuniary interest:	None

GDG meeting	Declaration of Interests	Action taken
Meeting (18 October 2013)	I have accepted an invitation from AMGEN to attend an advisory board on 5 November 2013 to discuss the development of a novel therapy for Familial Hypercholesterolaemia and I will deliver a short presentation on current management of severe FH, for which I will receive an honorarium.	
Eleventh GDG Meeting (22 November 2013)	Personal non-pecuniary interest: Participated in JBS3 on behalf of Heart UK on lipids produced 2 years ago. I will participate in a meeting on 4 December. I have also been involved in the production of lipid lowering guideline produced for the North East (FATS)	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Dr Nadeem Qureshi

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	Non-personal pecuniary interest: I have received research grants to assess the implementation of familial hypercholesterolemia in primary care, and the clinical utility of the family history in primary care. I have published in both areas. Personal non-pecuniary interest: I have published a paper on the primary care research evidence underpinning NICE guidelines. (Scullard et al. BJGP 2011) I am collaborating on an NIHR Research for Patient Benefit grant exploring the topic further.	None
First GDG meeting (11 September 2012)	No changes to record.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	Non-personal pecuniary interest: I am supervising a PhD looking at new metrics to assess risk prediction models. As part of this organising a CME sessions for General Practitioners on risk prediction models.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG	Non-personal pecuniary interest:	None

GDG meeting	Declaration of Interests	Action taken
Meeting (31 May 2013)	Supervising a PhD student studying new approaches to assess the role of novel markers on risk prediction algorithms, for example CV and osteoporosis. Published on quality of family history in GP datasets. CV lead for the vascular check programme in Derby city. Publishing a paper with a health economist about target versus universal	
Eight GDG Meeting (11 September 2013)	Non-personal pecuniary interest: I am supervising a PhD looking at new metrics to assess risk prediction models. As part of this organising a CME sessions for General Practitioners on risk prediction models. Published on quality of family history in GP datasets. Cardiovascular lead for the vascular check programme in Derby city PCT up to 2011. Writing a paper with a health economist about target versus universal CHD screening.	None
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	Personal non-pecuniary interest: I have been involved in 2 NICE guidelines – Familial Hypercholesterolemia & Familial Breast Cancer. I am on the quality standard group for Familial Hypercholesterolemia. I am also on the QAF group for NICE and lead their economics subgroup. In July 2014, I will give a talk on identifying FH at Heart UK.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Dr Alan Rees

GDG meeting	Declaration of Interests	Action taken
GDG recruitment	No Declaration of interest	None
First GDG meeting (11 September 2012)	Non-personal pecuniary interest: Previously been member of advisory board for MSD and Pfizer (12 months ago). Advisory board for Genzyme in the last 12 months. Previously received assistant to attend international meetings sponsorship. Personal non-pecuniary interest: Current president of section on Lipids and Vascular risk at the RSM. Ex-chair of heart UK – current trustee. Have written editorials/papers. Editor of sections of current opinion in Lipidology. Writing committee of IBS-3. FHGIT group. All Wales FH group. In discussion re trials for new drugs – Genzyme/Sanofi and Novartis.	None
Second GDG Meeting	Personal pecuniary interest – Recruit AD board for MSD – focused on ezetimibe. Recruit talk on new drugs in development for	None

GDG meeting	Declaration of Interests	Action taken
(24 October 2012)	Dyslipidemia.	
Third GDG Meeting (30 November 2012)	Personal pecuniary interest: Recently chaired a medical meeting on Diabetes, sponsored by AZ Pharmaceuticals	None
Fourth GDG Meeting (6 February 2013)	Personal pecuniary interest: I gave 2 lectures on 9 October 2012 (Midland Hotel, Manchester) and 10 October 2012 (London, Connaught Rooms) for Primed Educational Programmes. The Meeting was entitled Cardiac Commissioning Meeting and I gave a talk on New Drugs in the Pipeline for the Treatment of Dyslipidaemias. I received a speaker fee and travelling expenses. The Meeting was sponsored by MSD and organised by Primed Educational Programmes Ltd. On 21 November 2012 I attended the ABPI Wales Dinner in Cardiff as a guest of Abbott Healthcare. I gave a lecture on the forthcoming JBS3 Guidelines to the North West Lipid Forum on Tuesday 4 December 2012. I will receive travelling expenses and a speaker fee. The Meeting was sponsored by an educational grant from MSD. On 12 April 2013 I have been invited (and accepted) to attend a Sanofi Pharmaceutical Advisory Board. This is to advise on the development of a new monoclonal PCSK9 antibody for the treatment of severe hypercholesterolaemia. This product is not licensed but is under development. On Wednesday 27 February 2013 I have agreed to give a talk on Developing Diabetic Services in the Locality. I will receive a speaker fee. This lecture will not refer to any pharmaceutical product but is on the context of a day long symposium sponsored by Bristol Myers Squibb and AstraZeneca.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	Personal pecuniary interest: I have recently attended an Advisory Board for Lomitapide for which I received an honorarium. This drug is not licensed for use at present and is not considered in the NICE guideline we are currently developing. I have also attended an Advisory Board for Aegerion who are developing a monoclonal antibody for PCSK9. I also received an honorarium for this. However this is not licensed as yet and again is not under consideration for the current NICE guidelines. Personal non-pecuniary interest: Membership of JBS-3 guidelines development group including assessment of risk calculation systems. Membership of groups involved in implementation of CVD assessment risk tools in Wales.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None
Ninth GDG	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Meeting (12 September 2013)		
Tenth GDG Meeting (18 October 2013)	Non-personal pecuniary interest: I have acted as a paid member of an Advisory Board for Novartis who are developing a drug from chylomicronemia syndrome (not available at present and no relevance to the current NICE guidelines), and to Amgen who are developing a monoclonal antibody to PCSK9 but is not licensed at present. I have been asked to speak at a forthcoming meeting on diabetes which is sponsored by AstraZeneca but I am not promoting drug or any medication. I am principle investigator to 2 trials involving monoclonal antibody to PCSK9 and an antisense oligonucleotide to Apo B. I have recently given lectures to the Young Diabetes Forum and to a day long conference at the RSM on New Drugs in Development for the Treatment of Dyslipidaemia. None of these drugs are in clinical use or licensed at present. I have also sat on an advisory board organised and funded by Aegerion who are developing a drug for homozygous familial hypercholesterolemia Lomitapide.	None
Eleventh GDG Meeting (22 November 2013)	Non-personal pecuniary interest: Member of JBS-3 writing committee. Trustee of Heart-UK.	None
Twelfth GDG Meeting (04 April 2014)	No changes to record	None

Dr David Wald

GDG meeting	Declaration of Interests	Action taken
GDG recruitment 13/08/2012	Personal pecuniary interest I have an interest in the development of the Polypill which contains a statin. Personal non-pecuniary interest I am a Prinicipal Investigator of a Trial examining the effect of text message reminders on adherence to preventive cardiac treatment (including statins) which is partly funded by an education grant from Astra Zeneca. Updated January 2015	None
First GDG meeting (11 September 2012)	Personal non-pecuniary interest: Editorials and academic publications	None
Second GDG Meeting (24 October 2012)	Personal non-pecuniary interest: Academic publications.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG	No changes to record.	None

GDG meeting	Declaration of Interests	Action taken
Meeting (6 February 2013)		
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	Personal non-pecuniary interest: talk on FH	None
Seventh GDG Meeting (31 May 2013)	Personal non-pecuniary interest: Principal investigator for a trial of combination treatment for prevention of CVD; Wald DS, Morris JK, Wald NJ (2012) Randomized Polypill Crossover Trial in People Aged 50 and Over. PLoS ONE 7(7): e41297. doi:10.1371/journal.pone.0041297.	None
Declaration received on 1 July 2013	Personal pecuniary interest: I am a Director of Polypill Ltd that aims to develop a combination pill for the prevention of cardiovascular disease. Personal family interest: My father, Nicholas Wald is a Director of Polypill Ltd. Personal non-pecuniary interest: I have published and given lectures on the efficacy of cholesterol and blood pressure reduction in the general population in the prevention of cardiovascular disease. This includes a trial of combination treatment for prevention of CVD; Wald DS, Morris JK, Wald NJ (2012) Randomized Polypill Crossover Trial in People Aged 50 and Over. PLoS ONE 7(7): e41297. doi:10.1371/journal.pone.0041297	Withdrawn from the GDG.
Eight GDG Meeting (11 September 2013)	N/A	N/A
Ninth GDG Meeting (12 September 2013)	N/A	N/A
Tenth GDG Meeting (18 October 2013)	N/A	N/A
Eleventh GDG Meeting (22 November 2013)	N/A	N/A
Twelfth GDG Meeting (04 April 2014)	N/A	N/A

B.2 NCGC staff

NCGC staff

GDG meeting	Declaration of Interests	Action taken
First GDG meeting (11 September 2012)	Angela Cooper declared a personal non-pecuniary interest: Author on BMJ clinical evidence review secondary prevention of ischaemic cardiac events. Clinical Evidence 2011; 08-206.	None
Second GDG Meeting (24 October 2012)	No changes to record.	None
Third GDG Meeting (30 November 2012)	No changes to record.	None
Fourth GDG Meeting (6 February 2013)	No changes to record.	None
Fifth GDG Meeting (15 March 2013)	No changes to record.	None
Sixth GDG Meeting (24 April 2013)	No changes to record.	None
Seventh GDG Meeting (31 May 2013)	No changes to record.	None
Eight GDG Meeting (11 September 2013)	No changes to record.	None
Ninth GDG Meeting (12 September 2013)	No changes to record.	None
Tenth GDG Meeting (18 October 2013)	No changes to record.	None
Eleventh GDG Meeting (22 November 2013)	No changes to record.	None

B.3 Co-optees and peer reviewers

Dr Gary Collins

Date	Declaration of Interests	Action taken
31 May 2013	Personal pecuniary interest: In 2008 I (along with Professor Douglas Altman, University of Oxford) was commissioned by the Department of Health to independently verify the validation of QRISK conducted by Hippisley-Cox that was published in Heart and replicate an analysis conducted by the University of East Anglia, who attempted to reproduce the Hippisley-Cox validation published in Heart and failed. The report is available on the Department of Health website. I am the principal investigator of an MRC funded methodology grant using QRESEARCH and Framingham models as tools to demonstrate methodological aspects on how to validate prediction models, such as sample size requirements, handling of missing data and study design for validation studies. Personal non-pecuniary interest: I have published numerous papers and editorials on risk assessment tools including independent validations of QRISK, QRISK2 and Framingham published in the BMJ and Primary Care Cardiovascular Journal (these studies received no funding apart from the original validation of QRISK published in the BMJ 2009, which was funded as noted above in by the Department of Health). I have also independently validated other QRESEARCH models, including models for diabetes, osteoporotic and hip fracture, cancer, statin usage, and kidney disease (all received no funding). I am Head of Prognosis Methodology at the Centre for Statistics in Medicine, University of Oxford and therefore my main areas of research are in risk prediction, including the reporting of risk prediction models (including the development of reporting guidelines for journals, editors, reviewers and authors), evaluating risk of bias in studies developing and validating risk prediction models, systematic reviews of the methodological conduct and reporting of risk prediction models, developing guidance for authors of systematic reviews of prediction models and statistical and study design issues in developing and validating risk prediction models.	None

Ms Jo Farrington

Date	Declaration of Interests	Action taken
11 September 2013	Personal non-pecuniary interest: I am the Chair of the Cardiovascular and Respiratory Dietitians, a specialist interest group of the British Dietetic Association. We advise other members and the wider community id dietitians on hyperlipidaemia management and prevention.	None

Professor Rod Jackson

Date	Declaration of Interests	Action taken
2 August 2013	None.	None

Professor Joan Morris~~, Queen Mary University of London~~

Date	Declaration of Interests	Action taken
1 August 2013	Personal non-pecuniary interest: I have worked closely with Prof Sir Nicholas Wald on evaluating screening tests for IHD. We have published: Wald NJ, Simmonds M, Morris JK. Screening for future cardiovascular disease using age	None

Date	Declaration of Interests	Action taken
	alone compared with multiple risk factors and age. PLoS One. 2011;6:e18742.	

Professor Mark Simmonds

Date	Declaration of Interests	Action taken
1 August 2013	Personal non-pecuniary interest: Personal opinions on cardiovascular screening and treatment as published: see Wald, Simmonds, Morris. PloS One 2011: 6(5): e18742. Simmonds, Wald. J Med Screen 2012: 19(4).	None

Professor Liam Smeeth

Date	Declaration of Interests	Action taken
9 August2013	Personal pecuniary interest: I have undertaken paid consultancy work for GSK Non-personal pecuniary interest: I have received grant funding from the Wellcome Trust, MRC, BHF, NIHR, EU and other charitable or governmental organisations. My employing institution (LSHTM) has received funding from a very wide range of funders including industry.	None

Dr David Wheeler

Date	Declaration of Interests	Action taken
12 September 2013	Personal pecuniary interest: Consultancy fees: Amgen, Baxter. Honoraria: Astellas, Baxter, MSD, Viforpharma, Amgen, Otsuka, Fresenius and Shire. Non-personal pecuniary interest: Research grants: Genzyme and Abbott.	None

Appendix C: Review protocols

C.1 Bile acid sequestrants (anion-exchange resins)

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of bile acid sequestrants (anion-exchange resins) versus statin or placebo?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention/Comparison	• Anion-exchange resins versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Anion-exchange resins (+ statins) versus statins • Anion-exchange resins (no statin) versus placebo (no statin)
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • MI • Stroke or TIA (transient ischaemic attack) • Hospitalisation • Adverse events • Quality of life
Exclusion	If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered. Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only
Study design	RCTs, systematic reviews of RCTs
Review strategy	Sub groups (considered separately if studies available): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomics groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.2 Fibrates

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of fibrates versus statin or placebo?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of fibrates versus statin or placebo?	
	• Adults with CKD • Adults with established CVD
Intervention/Comparison	• Fibrates versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Fibrates (+ statins) versus statins • Fibrates (no statin) versus placebo (no statin)
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • MI • Stroke or TIA (transient ischaemic attack) • Hospitalisation • Adverse events • Quality of life
Exclusion	If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered. Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only
Study design	RCTs, systematic reviews of RCTs
Review strategy	Sub groups (considered separately if studies available): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomics groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.3 Nicotinic acids

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of nicotinic acids versus statin or placebo?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention/Comparison	• Nicotinic acids versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Nicotinic acids (+ statins) versus statins • Nicotinic acids (no statin) versus placebo (no statin)

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of nicotinic acids versus statin or placebo?	
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • MI • Stroke or TIA (transient ischaemic attack) • Hospitalisation • Adverse events • Quality of life
Exclusion	If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered. Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only
Study design	RCTs, systematic reviews of RCTs
Review strategy	Sub groups (considered separately if studies available): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomics groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.4 Omega-3 fatty acids

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of omega-3 fatty acids versus statin or placebo?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention/Comparison	• Omega-3 fatty acids versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Omega-3 fatty acids (+ statins) versus statins • Omega-3 fatty acids (no statin) versus placebo (no statin)
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • MI • Stroke or TIA (transient ischaemic attack) • Hospitalisation • Adverse events • Quality of life

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of omega-3 fatty acids versus statin or placebo?	
Exclusion	If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered. Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only
Study design	RCTs, systematic reviews of RCTs
Review strategy	Sub groups (considered separately if studies available): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomics groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.5 Diet

Review question	What is the clinical and cost effectiveness of dietary intervention strategies versus usual diet for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention/comparison	Diet versus no intervention or usual diet
Outcomes	• All-cause mortality • CV mortality • Non-fatal MI • Stroke • Quality of life
Exclusion	Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered.
Study design	RCTs, systematic reviews of RCTs
Review strategy	Analysis will be conducted on the following subgroups (considered separately if studies available): black and minority ethnic groups • people with a family history of CVD • low socioeconomic groups • people aged 75 years and over • women • people with autoimmune disease

Review question	What is the clinical and cost effectiveness of dietary intervention strategies versus usual diet for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?
	• people with serious mental illness

C.6 Phytosterol (stanol and sterol) –enriched foods

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of phytosterol (stanol and sterol)-enriched foods or supplements versus statin or placebo?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention/Comparison	• Phytosterol (stanol and sterol)-enriched foods or supplements versus placebo
Outcomes	• All-cause mortality • CV mortality • Non-fatal MI • Stroke • Quality of life
Exclusion	If, during sifting of the abstract lists, the RCT abstract does not mention CVD outcomes it will not be ordered. Follow-up <1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only
Study design	RCTs, systematic reviews of RCTs
Review strategy	Sub groups (considered separately if studies available): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomics groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.7 Risk assessment tools

Review questions: Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?	
Population	Adults (18 years and over) without established CVD, including adults with CKD
Index tests (risk assessment tools)	• QRISK 2 • Framingham(validated in the UK) • Age alone
Reference standard or target conditions	CVD events: • All-cause mortality

Review questions: Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?	
	• CV mortality • Non-fatal MI • Stroke
Outcomes (in terms of discrimination/calibration)	• Area under the ROC curve (c-index, c-statistic). • Sensitivity, specificity, predictive values at 5%, 10%, 15% and 20% threshold. • Predicted risk versus observed risk (calibration). • Other outcomes: for example, D statistic, R2 statistic and Brier score. • Reclassification (Note: for all outcomes, need to consider short term versus long term measures)
Inclusion criteria and study types	• Cohort studies • RCTs • Systematic reviews
Exclusions	• Case-control studies • Cross-sectional studies • CVD events reported in study (event rate) < 100

C.8 Risk assessment tools (people with diabetes)

Review questions: Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?	
Population	• Adults with type 1 diabetes (without established CVD) • Adults with type 2 diabetes (without established CVD)
Index tests (risk assessment tools)	• QRISK 2 • UKPDS Risk Engine • Age alone
Reference standard or target conditions	CVD events: • All-cause mortality • CV mortality • Non-fatal MI • Stroke
Outcomes (in terms of discrimination/calibration)	• Area under the ROC curve (c-index, c-statistic). • Sensitivity, specificity, predictive values at 5%, 10%, 15% and 20% threshold. • Predicted risk versus observed risk (calibration). • Other outcomes: for example, D statistic, R2 statistic and Brier score. • Reclassification (Note: for all outcomes, need to consider short term versus long term measures)
Inclusion criteria and study types	• Cohort studies • RCTs • Systematic reviews
Exclusions	• Case-control studies

Review questions: Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?	
	• Cross-sectional studies • CVD events reported in study (event rate) < 100

C.9 Prediction of statin adverse effects

Review question: Who is at risk of adverse effects from statin treatment? (Are some subgroups at different risk of adverse events?)	
Population	Adults (18 years and over) on statin therapy (Simvastatin, Atorvastatin, Rosuvastatin, Pravastatin, Fluvastatin) as one class
Prognostic factors	Any
Outcomes	• Rhabdomyolysis (CK>10 times normal) • Myalgia • Liver (transaminases>3 times normal level) • New onset diabetes
Exclusion	• Papers without a multivariable analysis • Case-control studies • Retrospective
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. All years.
Study design	Cohort studies

Review strategy	• Determine from the GDG what are the key confounders for each outcome.
	• Start with the 'best' study (high n. of events per covariate and key confounders included)
	• Data to be extracted for analysis includes:
	  ○ Definition of predictor present versus predictor absent ('referent') where categorical/dichotomous predictor (for example, age over 75 years versus age under 60 years) or statement that continuous predictor (for example, age per year)
	  ○ OR (95% CI) or HR (95% CI)
	  ○ Type of analysis (cox regression, logistic regression)
	  ○ Method of multivariable analysis (for example, all significant univariate predictors included)
	  ○ List of all covariates included in the multivariable analysis
	  ○ Number of events
	• Time when the event occurs since starting of statin therapy
	• Enter data into RevMan using the generic inverse variance method
	• Show forest plot and don't meta-analyse, but look at trends
	• For GRADE table report median (with its 95% CI) and the range across studies
	• Statistical significance following multivariable analysis is the way to determine whether the risk factor is an independent predictor of the outcome

C.10 Adherence to statin therapy

Review question	What is the clinical and cost effectiveness of interventions that improve adherence to statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?
Objectives	To estimate the effectiveness and cost effectiveness of interventions which may improve patient adherence to statin medication
Population	Adults prescribed statins
Intervention	• Coenzyme Q_{10} (ubidecarenone, ubiquinone, CoQ10) • Vitamin D
Comparison	Placebo
Outcomes	• Adherence • Quality of life
Study design	RCTs, systematic reviews of RCTs
Search	The databases to be searched are Medline, Embase, and The Cochrane Library. Studies will be restricted to English language only. All years.
Review strategy	Analysis will be conducted on the following subgroups (considered separately if studies available): • black and minority ethnic groups • people with a family history of CVD • low socioeconomic groups • people aged 75 years and over • women • people with autoimmune disease • people with serious mental illness.

C.11 Efficacy of statin therapy

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention) what is the clinical and cost effectiveness of statin therapy?	
Population	All adults (18 years and over) including: • Adults without established CVD • Adults with type 1 diabetes • Adults with type 2 diabetes • Adults with CKD • Adults with established CVD
Intervention	Statins (all together as one class): • Simvastatin • Atorvastatin • Rosuvastatin • Pravastatin • Fluvastatin
Comparison	• Low intensity groups (pravastatin 10–40 mg or equivalent) • Medium intensity (simvastatin 40 mg or equivalent) • High intensity group (atorvastatin 80 mg or equivalent) • Placebo
Outcomes	• All-cause mortality

Review question: For adults without established CVD (primary prevention) and with established CVD (secondary prevention) what is the clinical and cost effectiveness of statin therapy?	

	• CV mortality
	• Non-fatal MI
	• Stroke
	• Quality of life
	• LDL-cholesterol reduction
	• Adverse events:
	  ○ Rhabdomyolysis (CK >10 times normal)
	  ○ Myalgia
	  ○ Liver disfunction (transaminases >3 times normal level)
	  ○ New onset diabetes

Exclusion	Follow up < 1 year
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library. Studies will be restricted to English language only. All years.
Study design	RCTs, systematic reviews of RCTs
The review strategy	Subgroups (considered to explain heterogeneity): • Black and minority ethnic groups • People with a family history of CVD • Low socioeconomic groups • People aged 75 years and over • Women • People with autoimmune disease • People with serious mental illness

C.12 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[(a)] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[1009] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will

	usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix K. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, USA, Switzerland) • non-OECD settings (always 'Not applicable'). *Economic study type:* • cost–utility analysis • other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis) • comparative cost analysis • non-comparative cost analyses including cost-of-illness studies (always 'Not applicable'). *Year of analysis:* • The more recent the study, the more applicable it is. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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

Appendix D: Clinical article selection

Figure 1: Flow diagram of clinical article selection for the review of risk assessment tools

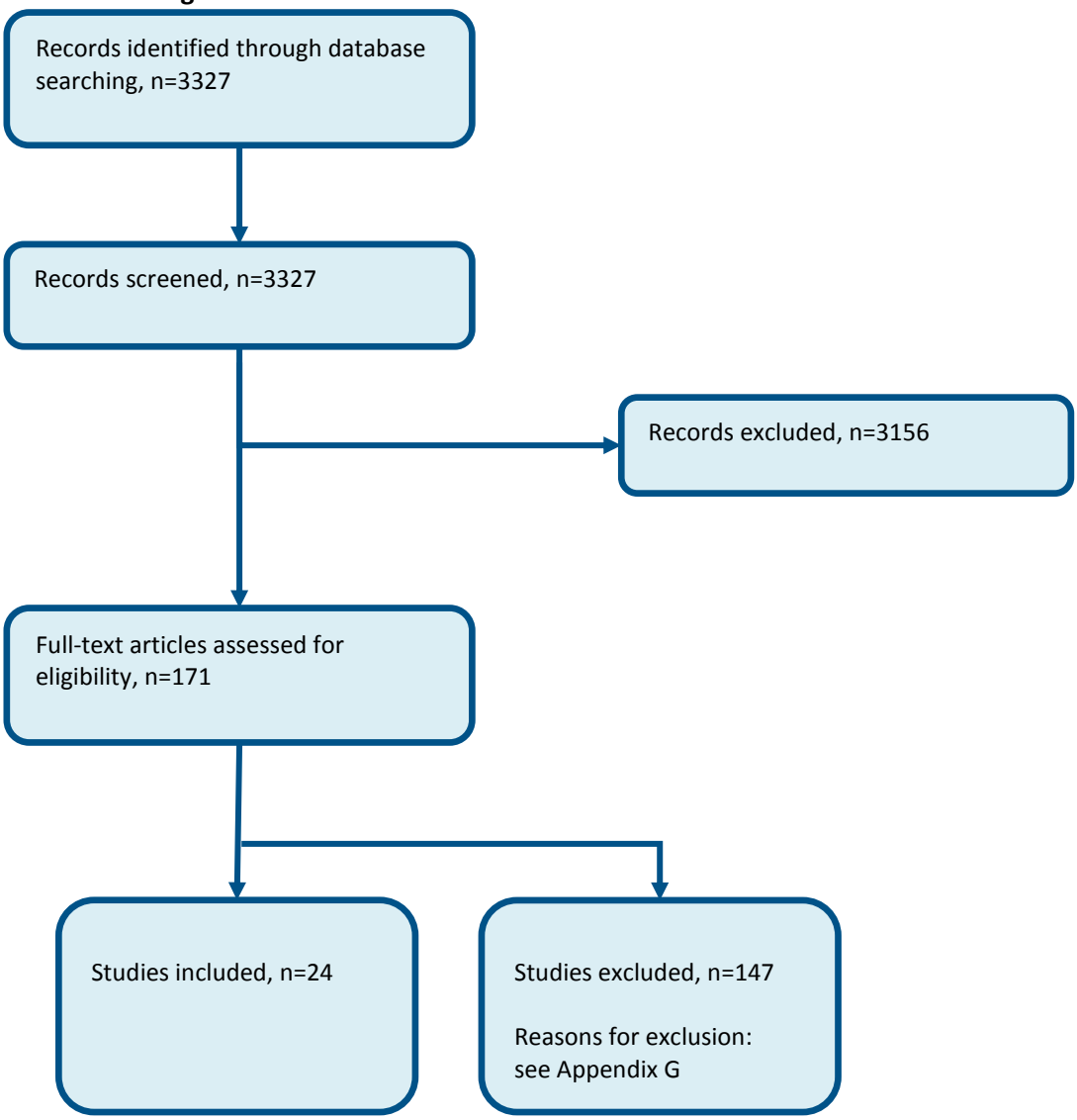


Figure 2: Flow chart of clinical article selection for the review of dietary interventions

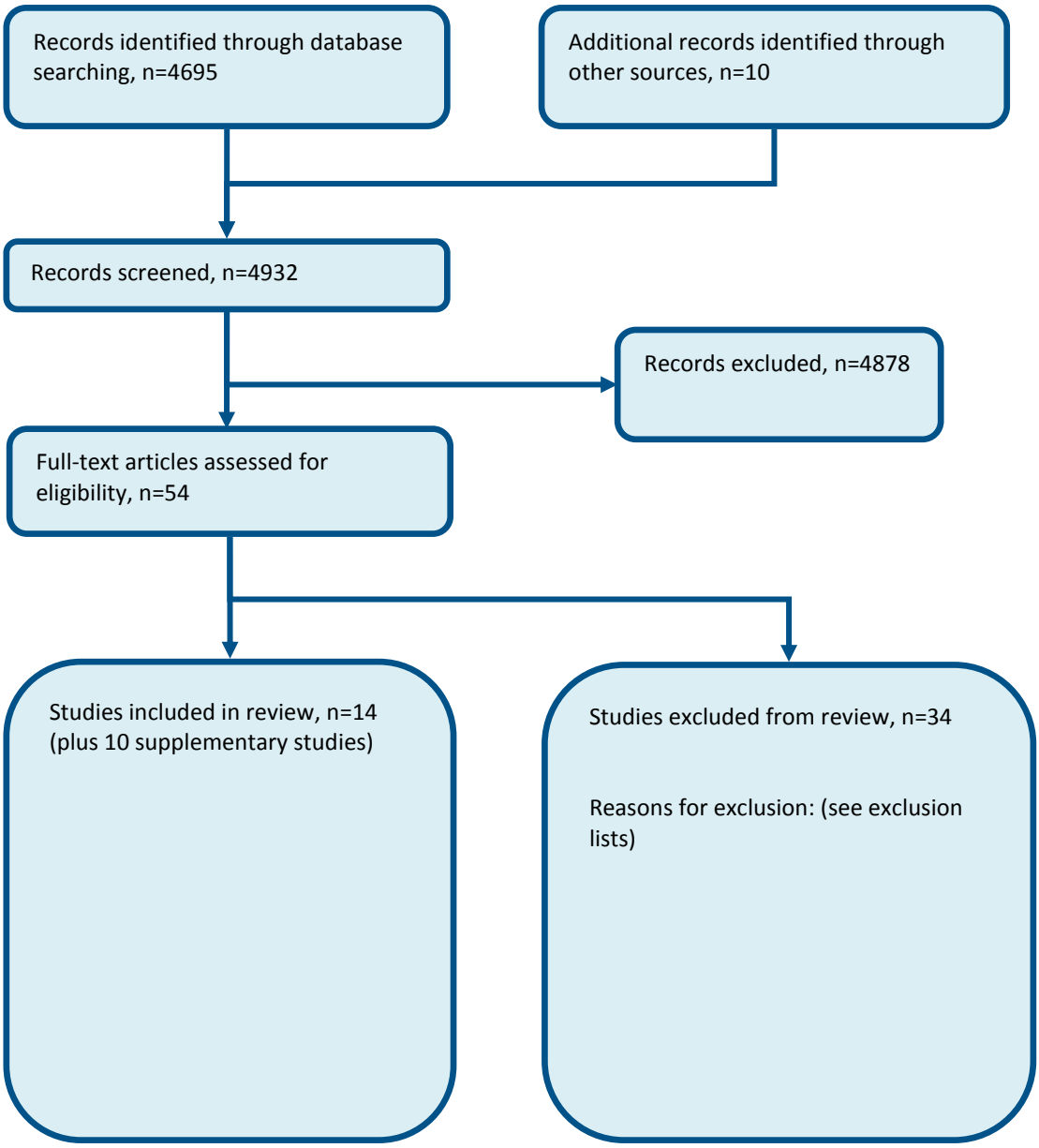


Figure 3: Flow diagram of clinical article selection for the review of foods enriched with phytosterols (plant stanols and sterols)

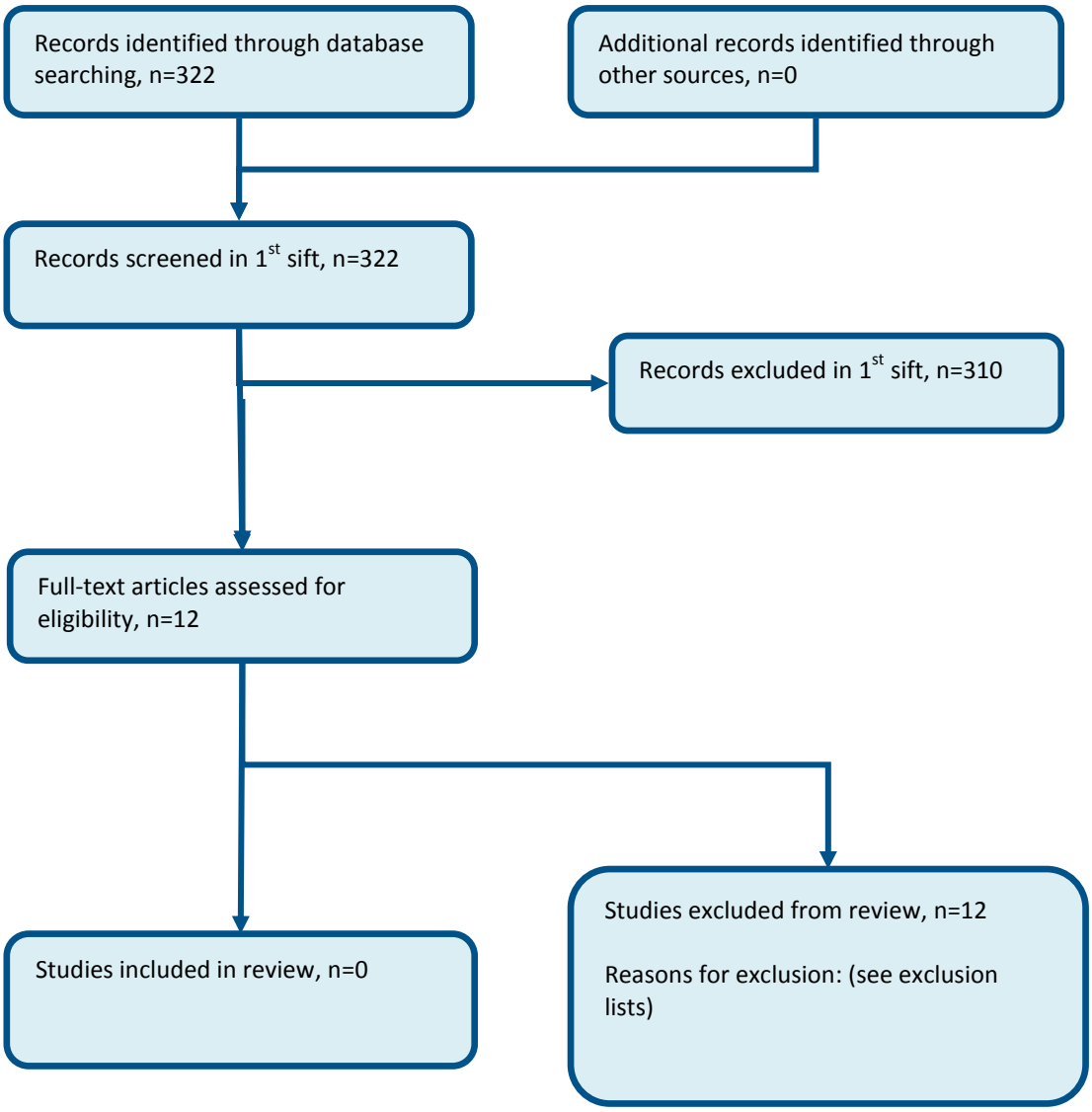


Figure 4: Flow chart of clinical article selection for the review of statin efficacy and LDL-cholesterol reduction

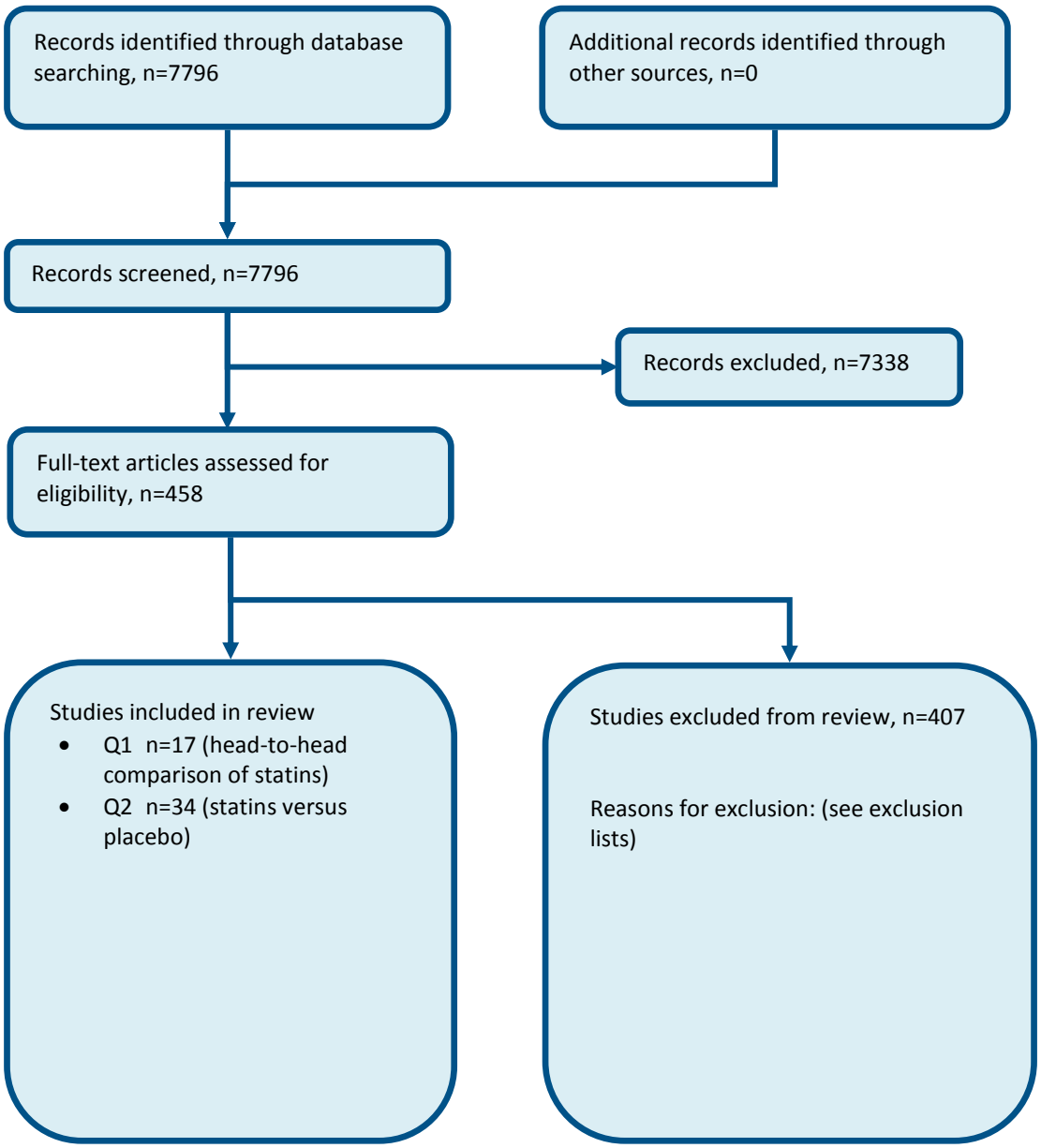


Figure 5: Flow chart of clinical article selection for the review of interventions to improve adherence to statin therapy

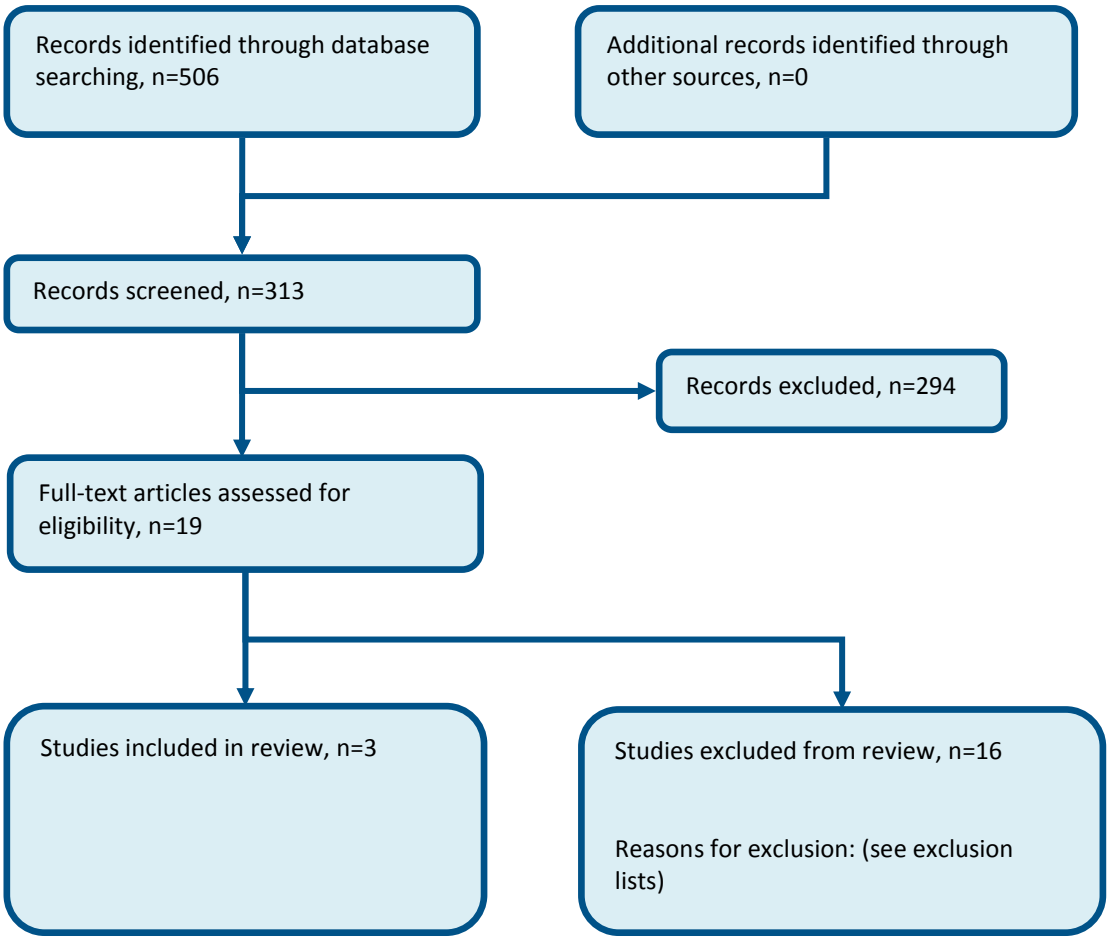


Figure 6: Flow chart of clinical article selection for the review of subgroups at risk of adverse events

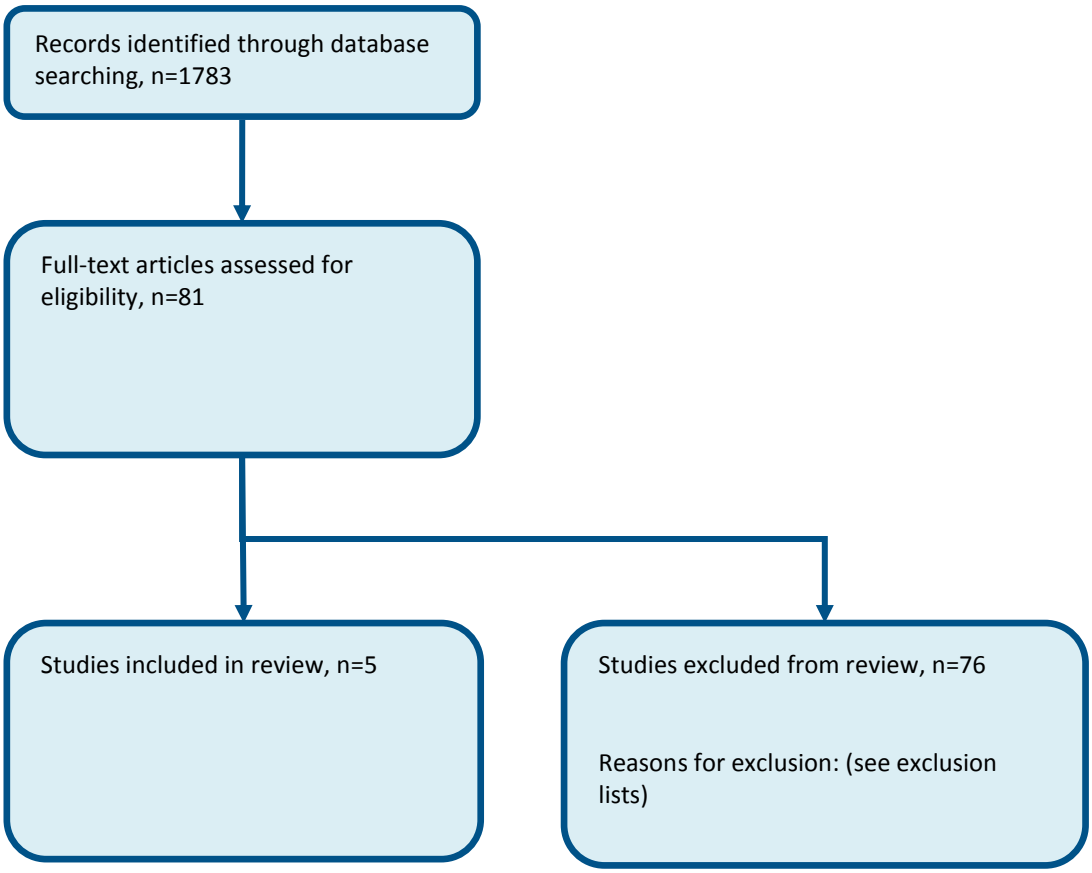


Figure 7: Flow chart of clinical article selection for the review of fibrates

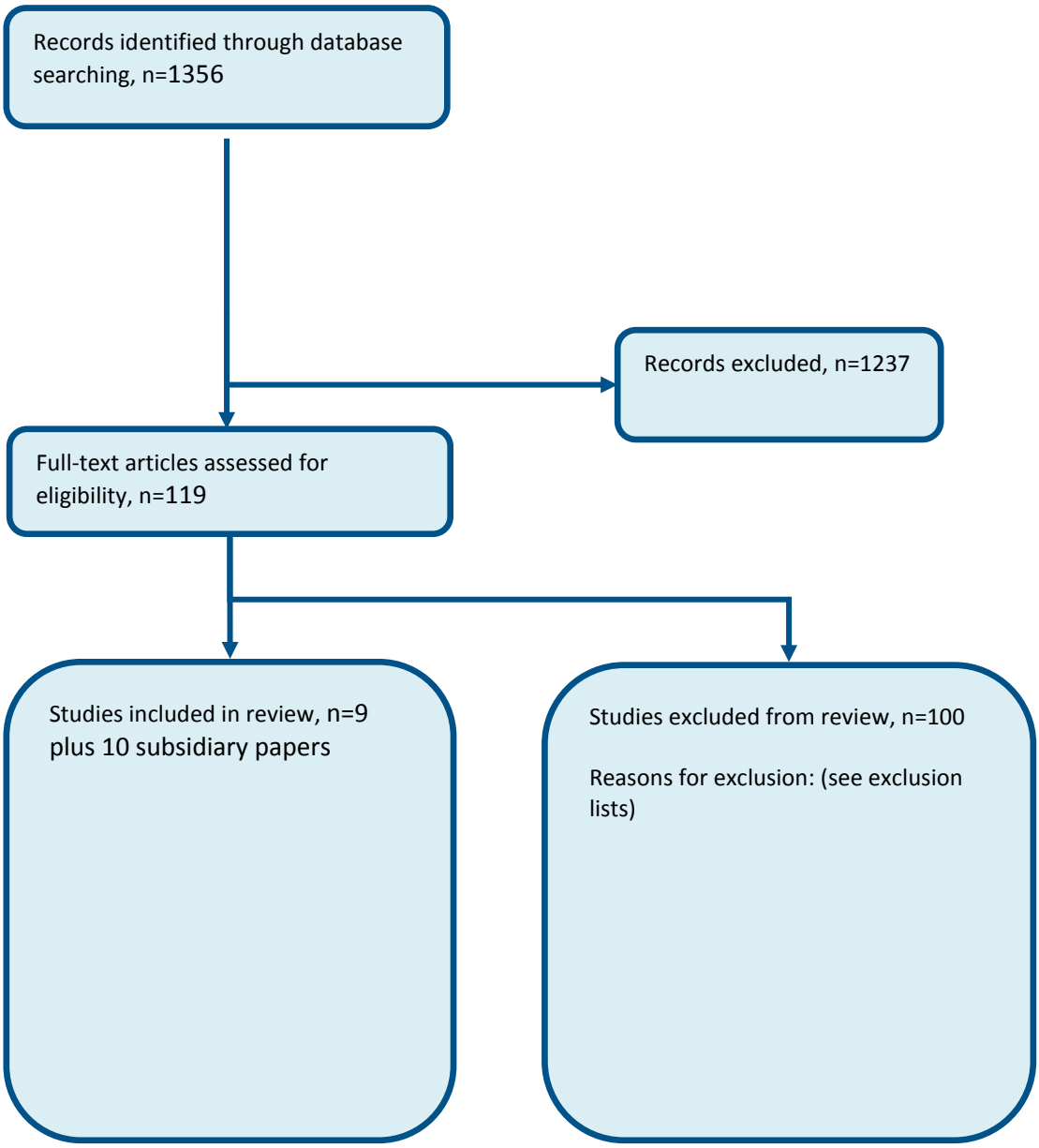


Figure 8: Flow chart of clinical article selection for the review of nicotinic acids

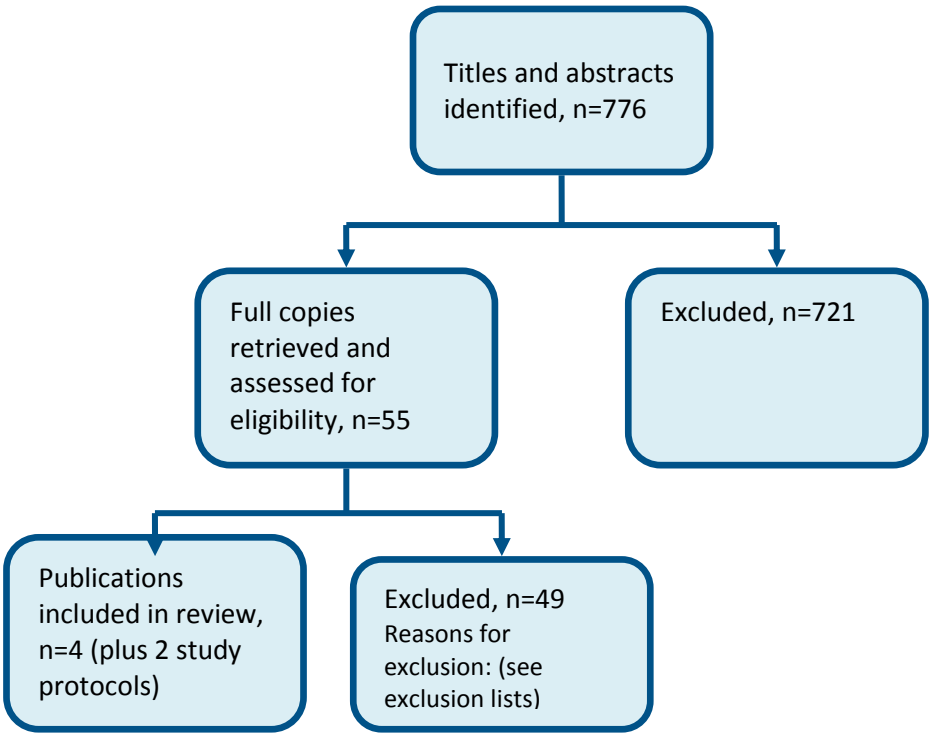


Figure 9: Flow chart of clinical article selection for the review of bile acid sequestrants

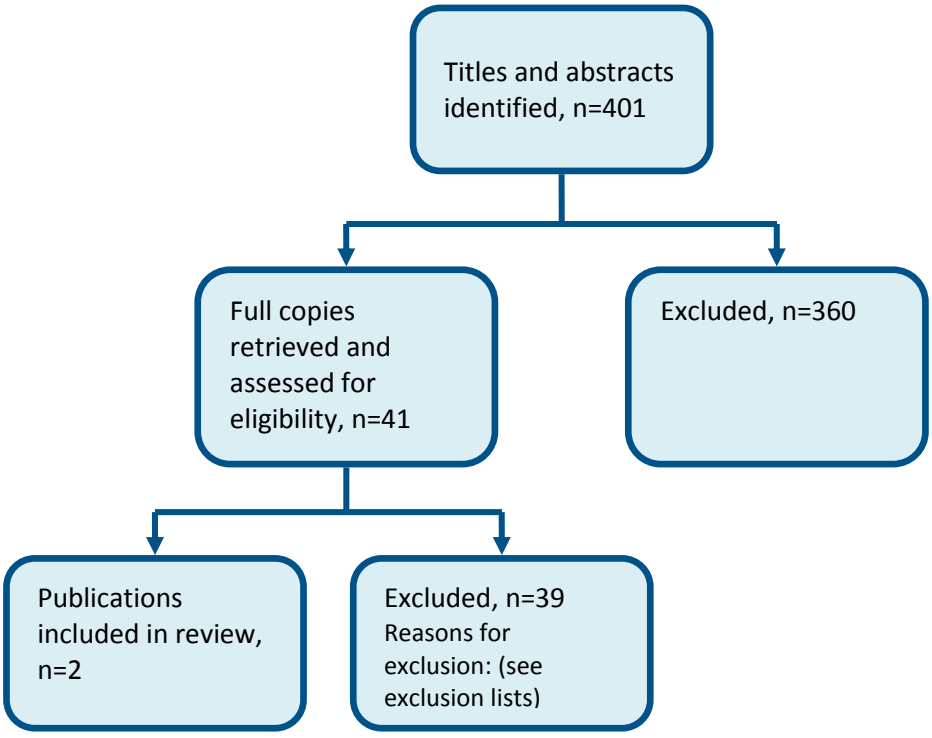
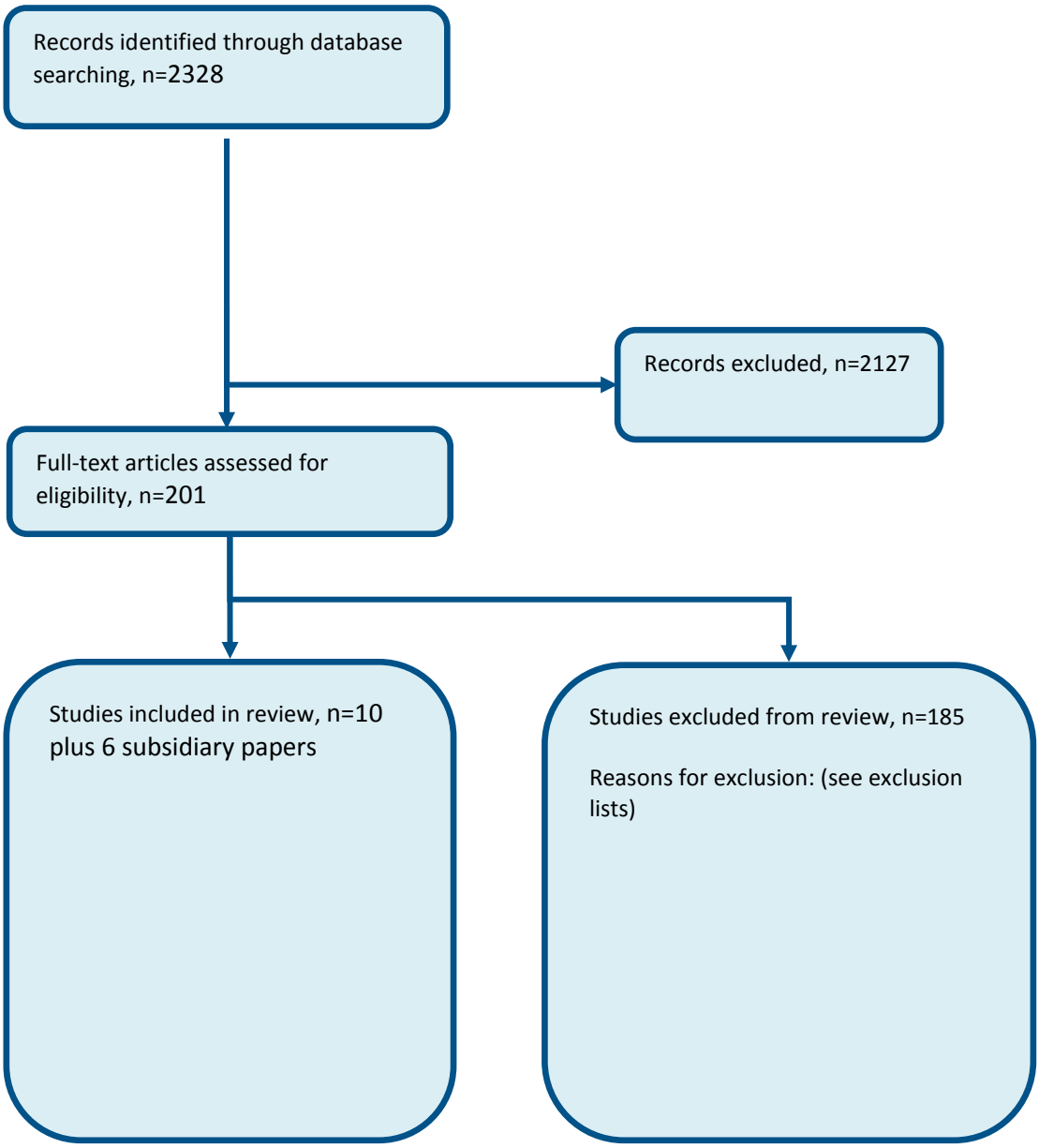
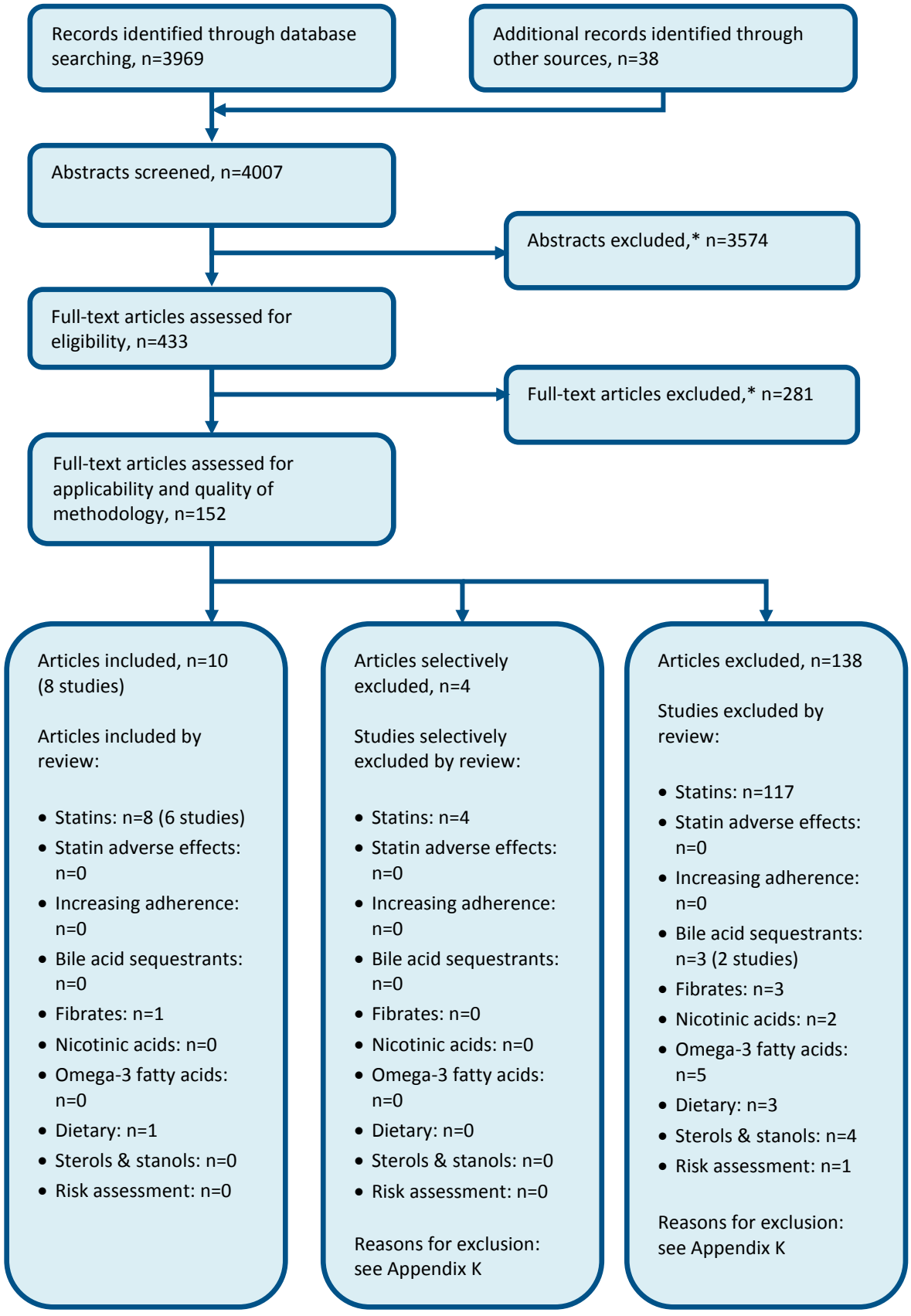


Figure 10: Flow chart of clinical article selection for the review of omega-3 fatty acids



Appendix E: Economic article selection

Table 1: Flow chart of economic article selection for the guideline



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

Appendix F: Literature search strategies

Contents

Search strategies used for the Lipid modification guideline were run in accordance with the NICE Guidelines Manual 2012: http://publications.nice.org.uk/the-guidelines-manual-pmg6/

All searches were run up to **11/12/13** unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Table 1: Database date parameters (unless otherwise stated)

Database	Searched
Medline	All years – 11/11/2013
Embase	All years – 11/11/2013

Database	Searched
AMED	All years – 11/11/2013
The Cochrane Library	Cochrane Reviews to 2013 Issue 11 of 12 CENTRAL to 2013 Issue 11 of 12 DARE, HTA and NHSEED to 2013 Issue 4 of 4

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

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

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

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

All searches in Medline and Embase had a filter added to exclude animal studies and papers relating to comments, letters and editorials.

F.1 Population search strategies

F.1.1 CVD population

Medline search terms

1.	cardiovascular diseases/
2.	heart diseases/
3.	myocardial ischemia/
4.	exp angina pectoris/
5.	coronary disease/
6.	coronary artery disease/
7.	exp coronary stenosis/
8.	myocardial infarction/
9.	exp heart failure/
10.	arrhythmias, cardiac/ or atrial fibrillation/
11.	vascular diseases/
12.	hypertension/
13.	atherosclerosis/
14.	peripheral arterial disease/
15.	peripheral vascular diseases/

16.	cerebrovascular disorders/
17.	exp stroke/
18.	exp brain ischemia/
19.	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$)).ti,ab.
20.	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$)).ti,ab.
21.	(mi or myocardial infarct$).ti,ab.
22.	(cvd or chd or cad or pad or cva or hypertension).ti.
23.	(atheroscleros$ or arterioscleros$).ti,ab.
24.	(cerebrovascular accident$ or stroke$).ti,ab.
25.	(acs or angina or acute coronary syndrome$).ti,ab.
26.	(af or atrial fibrillation).ti,ab.
27.	((chronic or congestive) adj2 heart failure).ti,ab.
28.	or/1-27

Additional search terms were added to Medline populations as below:

Questions 1, 2, 7 and 10

1	exp heart arrest/
2	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
3	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
4	((heart or cardiopulmonary or cardiac) adj3 (death$ or arrest$ or attack$)).ti,ab.
5	(CVD or CHD or CAD or PAD or CVA).ti,ab.
6	(hypertension or hypertensive$).ti,ab.
7	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.

Questions 3 and 4

1	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
2	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
3	(CVD or CHD or CAD or PAD or CVA).ti,ab.
4	(hypertension or hypertensive$).ti,ab.
5	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.

Embase search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/

9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	*brain infarction/
21.	*atherosclerosis/
22.	exp *cardiovascular risk/
23.	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$)).ti,ab.
25.	(MI or myocardial infarct$).ti,ab.
26.	(CVD or CHD or CAD or PAD or CVA or hypertension).ti.
27.	(atheroscleros$ or arterioscleros$).ti,ab.
28.	(cerebrovascular accident$ or stroke$).ti,ab.
29.	(ACS or angina or acute coronary syndrome$).ti,ab.
30.	(AF or atrial fibrillation).ti,ab.
31.	((chronic or congestive) adj2 heart failure).ti,ab.

Additional search terms were added to Embase populations as below:

Questions 1, 2, 6, 7 and 10

1.	exp *heart arrest/ or *heart death/
2.	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
3.	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
4.	((heart or cardiopulmonary or cardiac) adj3 (death$ or arrest$ or attack$)).ti,ab.
5.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
6.	(hypertension or hypertensive$).ti,ab.
7.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.

Questions 3 and 4

1.	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
2.	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
3.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
4.	(hypertension or hypertensive$).ti,ab.
5.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.

Cochrane search terms

1	MeSH descriptor: [Cardiovascular Diseases] this term only
2	MeSH descriptor: [Heart Diseases] this term only
3	MeSH descriptor: [Myocardial Ischemia] this term only
4	MeSH descriptor: [Angina Pectoris] explode all trees
5	MeSH descriptor: [Coronary Disease] this term only
6	MeSH descriptor: [Coronary Artery Disease] this term only
7	MeSH descriptor: [Coronary Stenosis] explode all trees
8	MeSH descriptor: [Myocardial Infarction] this term only
9	MeSH descriptor: [Heart Failure] explode all trees
10	MeSH descriptor: [Arrhythmias, Cardiac] this term only
11	MeSH descriptor: [Vascular Diseases] this term only
12	MeSH descriptor: [Atrial Fibrillation] this term only
13	MeSH descriptor: [Hypertension] this term only
14	MeSH descriptor: [Atherosclerosis] explode all trees
15	MeSH descriptor: [Peripheral Vascular Diseases] this term only
17	MeSH descriptor: [Cerebrovascular Disorders] this term only
18	MeSH descriptor: [Stroke] explode all trees
19	MeSH descriptor: [Brain Ischemia] explode all trees
20	((cardiovascular or cardio-vascular or "cardio vascular" or coronary or heart or "peripheral arterial" or "peripheral vascular") near/3 (event* or disease* or disorder* or risk* or benefit*)):ti,ab
21	(CVD or CVA or CHD or PAD or CAD):ti,ab
22	(myocardial next infarct*):ti,ab
23	(MI or hypertension or hypertensive* or atheroscleros* or arterioscleros*):ti,ab
24	((high or raised or elevated) near/2 ("blood pressure" or bp)):ti,ab
25	(cerebrovascular next accident*):ti,ab
26	(stroke* or ACS or angina or AF or "atrial fibrillation"):ti,ab
27	("acute coronary" next syndrome*):ti,ab
28	((chronic or congestive) next ("heart failure")):ti,ab
29	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

Additional search terms were added to Cochrane populations as below:

Question 1 and 10

1	MeSH descriptor: [Heart Arrest] explode all trees
2	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab

Questions 2, 5, 6 and 7

1	MeSH descriptor: [Heart Arrest] explode all trees
2	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab
3	(heart or coronary or cardio* or cardiac* or athersclero* or arteriosclero* or ischemi* or ischaemi* or myocardi* or atrial* or infarct* or vascular or stenos* or hypertens* or cerebrovascular*):ti,ab

AMED search terms

1	exp cardiovascular disease/
2	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
3	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
4	(MI or myocardial infarct$).ti,ab.
5	(CVD or CHD or CAD or PAD or CVA).ti,ab.
6	(hypertension or hypertensive$).ti,ab.
7	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
8	(atherosclero$ or arteriosclero$).ti,ab.
9	(cerebrovascular accident$ or stroke$).ti,ab.
10	(ACS or angina or acute coronary syndrome$).ti,ab.
11	(AF or atrial fibrillation).ti,ab.
12	((chronic or congestive) adj2 heart failure).ti,ab.
13	(heart or coronary or cardio$ or cardiac$ or atherosclero$ or arteriosclero$ or ischemi$ or ischaemi$ or myocardi$ or atrial$ or infarct$ or vascular or stenos$ or hypertens$ or cerebrovascular).ti,ab.
14	or/1-13

Additional search terms added to AMED populations as below:

Question 2

1	exp heart disease/
2	exp myocardial ischemia/
3	exp angina pectoris/
4	exp coronary disease/
5	exp myocardial infarction/
6	exp heart failure congestive/
7	exp arrhythmia/
8	exp atrial fibrillation/
9	exp vascular disease/
10	exp hypertension/
11	exp arteriosclerosis/
12	exp cerebrovascular disorders/
14	exp stroke/
15	exp cerebral ischemia/
16	exp heart arrest/

F.2 Study filter search terms

F.2.1 Excluded studies designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

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

Embase search terms

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

Amed search terms

1	letter/
2	editorial/
3	news/
4	exp historical article/
5	anecdotes as topic/
6	comment/
7	case report/
8	(letter or comment*).ti.
9	or/1-8
10	randomized controlled trial/ or random*.ti,ab.
11	9 not 10
12	animals/
13	exp animals, laboratory/
14	exp animal experimentation/
15	exp models, animal/
16	exp rodentia/
17	(rat or rats or mouse or mice).ti.
18	humans/ or (men or man or human).ti.
19	(12 or 13 or 14 or 15 or 16 or 17) not 18
20	11 or 19

F.2.2 Systematic review (SR) search terms

Medline search terms

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

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.

8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Amed search terms

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

F.2.3 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	clinical trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

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

Amed search terms

1	randomized controlled trial.pt.

2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	clinical trials as topic.sh.
7	trial.ti.
8	or/1-7

F.2.4 Observational (OBS) studies

F.2.5 Medline search terms

1	Epidemiologic studies/
2	exp Case control studies/
3	exp Cohort studies/
4	Cross-sectional studies/
5	case control.ti,ab.
6	(cohort$ or case series or clinical series).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	Clinical study/
2	exp Case control study/
3	Family study/
4	Longitudinal study/
5	Retrospective study/
6	Prospective study/
7	Cross-sectional study/
8	Cohort analysis/
9	Follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort$ or case series or clinical series).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

F.2.6 Risk/statistical analysis (RISK)

Medline search terms

1	exp risk/

2	proportional hazards models/
3	multivariate analysis/
4	Adverse Drug Reaction Reporting Systems/
5	(risk$ adj2 (factor$ or benefit$ or relative or assessment)).ti,ab.
6	or/1-5

Embase search terms

1	(risk adj2 (assessment or relative or benefit$ or factor$)).ti,ab.
2	risk/ or risk assessment/ or risk factor/ or drug surveillance program/
3	multivariate analysis/ or proportional hazards model/
4	or/1-3

F.2.7 Economic (HE) studies

Medline search terms

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

Embase search terms

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

12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

F.2.8 Quality of life and model (QoL) search terms

Medline search terms

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

Embase search terms

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

18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

F.3 Searches by specific questions

F.3.1 Anion exchange resins

Q. For adults without established CVD (primary prevention) and with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of Anion-exchange resins?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD With additional lines	Anion exchange resins		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1	exp anion exchange resins/
2	((anion exchange or anionic exchange) adj2 resin*).ti,ab.
3	((anion or anionic) adj2 exchanger*).ti,ab.
4	(cholestyramin* or colestyramin* or colestimide or cholybar or colextran or colestilan or cholestagel or cholestipol or colestipol or colestid or questran* or quantalan* or cuemid* or colesevelam).ti,ab.
5	(bile acid adj3 (sequestrant* or sequestering agent* or resin*)).ti,ab.
6	or/1-5

Embase search terms

1	exp *anion exchange resin/
2	exp *bile acid sequestrant/
3	*colestilan/ or *colestipol/ or *colestyramine/ or *colesevelam/ or *diethylaminoethyldextran/
4	((anion exchange or anionic exchange) adj2 resin*).ti,ab.
5	((anion or anionic) adj2 exchanger*).ti,ab.
6	(cholestyramin* or colestyramin* or colestimide or cholybar or colextran or colestilan or cholestagel or colestipol or cholestipol or colestid or questran* or quantalan* or cuemid* or colesevelam).ti,ab.
7	(bile acid adj3 (sequestrant* or sequestering agent* or resin*)).ti,ab.
8	or/1-7

Cochrane search terms

1	MeSH descriptor Anion Exchange Resins explode all trees
2	(("anion exchange" or "anionic exchange") near/2 resin*):ti,ab
3	((anion or anionic) next exchanger*):ti,ab
4	(cholestyramin* or colestyramin* or colestimide or cholyber or colextran or colestilan or

	cholestagel or colestipol or cholestipol or colestid or questran* or quantalan* or cuemid or colesevelam):ti,ab
5	("bile acid" near/3 (sequestrant* or "sequestering agent" or "sequestering agents" or resin*)):ti,ab
6	#1 or #2 or #3 or #4 or #5

F.3.2 Dietary intervention

Q. What is the clinical and cost effectiveness of dietary intervention strategies versus usual diet in primary and secondary prevention of CVD?

This question was run as 2 separate searches.

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD not child or adolescent With additional lines	Dietary intervention		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1	exp diet, Mediterranean/
2	(Mediterranean adj3 diet*).ti,ab.
3	(Mediterranean adj6 food*).ti,ab.
4	(Mediterranean adj6 nutrition*).ti,ab.
5	(Mediterranean adj6 eat*).ti,ab.
6	exp *dietary fats, unsaturated/
7	*diet/
8	*diet therapy/
9	(diet* adj2 (therap* or change* or intervention* or treatment*)).ti,ab.
10	(diet* adj2 (lipid* or cholesterol)).ti,ab.
11	exp *plant oils/
12	olive oil.ti,ab.
13	or/1-12
14	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
15	13 not 14

Embase search terms

1	exp diet, Mediterranean/
2	(Mediterranean adj3 diet*).ti,ab.
3	(Mediterranean adj6 food*).ti,ab.
4	(Mediterranean adj6 nutrition*).ti,ab.
5	(Mediterranean adj6 eat*).ti,ab.
6	exp *dietary fats, unsaturated/
7	*diet/
8	*diet therapy/
9	(diet* adj2 (therap* or change* or intervention* or treatment*)).ti,ab.

10	(diet* adj2 (lipid* or cholesterol)).ti,ab.
11	exp *plant oils/
12	olive oil.ti,ab.
13	or/1-12
14	((child* or adolescen* or school* or infant* or teen* or paediatric* or pediatric* or youth*) not adult*).ti.
15	13 not 14

Cochrane search terms

1	MeSH descriptor: [Diet, Mediterranean] explode all trees
2	Mediterranean near/3 diet
3	Mediterranean near/6 food
4	Mediterranean near/6 nutrition
5	Mediterranean near/6 eat
6	MeSH descriptor: [Dietary Fats, Unsaturated] this term only
7	MeSH descriptor: [Diet] this term only
8	MeSH descriptor: [Diet Therapy] this term only
9	diet near/2 (therap* or change* or intervention* or treatment*):ti,ab
10	diet near/2 (lipid* or cholesterol):ti,ab
11	MeSH descriptor: [Plant Oils] this term only
12	olive oil:ti,ab
13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

F.3.3 Fibrates

Q. a) For adults without CVD (primary prevention), what is the clinical and cost effectiveness of fibrates versus placebo (or versus statin)?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD	Fibrates with and without statins		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1.	exp fibric acids/
2.	(fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modalim or ciprofibrate).ti,ab.
3.	((fibric or fenofibric or clofibric) adj2 acid*).ti,ab.
4.	or/1-4

Embase search terms

1.	exp *fibric acid derivative/
2.	((fibric or fenofibric or clofibric) adj2 acid*).ti,ab.
3.	(fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modalim or ciprofibrate).ti,ab.

4.	1 or 2 or 3

Cochrane search terms

1.	MeSH descriptor Fibric Acids explode all trees
2.	((fibric or clofibric or fenofibric) next acid*):ti,ab
3.	(fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modim or ciprofibrate):ti,ab
4.	#1 or #2 or #3

F.3.4 Nicotinic acids

Q. For adults without CVD (primary prevention), what is the clinical and cost effectiveness of Nicotinic acid versus placebo (or versus statin)?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD	Nicotinic acids		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1.	nicotinic acids/ or niacin/
2.	nicotinic.ti,ab.
3.	niacin.ti,ab.
4.	(nicotinate* or acipimox or acipemox).ti,ab.
5.	(olbetam or niaspan or tredaptive).ti,ab.
6.	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.
7.	or/1-6

Embase search terms

1.	*nicotinic acid/ or *laropiprant plus nicotinic acid/ or *acipimox/
2.	nicotinic.ti,ab.
3.	(niacin or nicotinate* or acipimox or acipemox or olbetam or niaspan or tredaptive).ti,ab.
4.	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.
5.	or/1-4

Cochrane search terms

1.	MeSH descriptor Nicotinic Acids, this term only
2.	MeSH descriptor Niacin, this term only
3.	(nicotinic or niacin or nicotinate* or niaspan or olbetam or tredaptive or acipimox or acipemox):ti,ab
4.	#1 or #2 or #3

F.3.5 Omega-3 fatty acids

Q. For adults with established CVD (secondary prevention), what is the clinical evidence and cost effectiveness of omega-3 fatty acids?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD With additional lines	Omega-3 fatty acids, statins and placebo		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1.	exp fish oils/
2.	fatty acids, unsaturated/ or exp fatty acids, omega-3/
3.	dietary fats, unsaturated/
4.	(fish adj3 oil*).ti,ab.
5.	(omega 3 or omega-3).ti,ab.
6.	((n 3 or n3 or n-3) adj3 ((fatty adj3 acid*) or PUFA*)).ti,ab.
7.	((docosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid*).ti,ab.
8.	(linolenate or maxepa or omacor).ti,ab.
9.	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA* or fatty acid*)).ti,ab.
10.	or/1-9

Embase population

1.	fish oil/
2.	polyunsaturated fatty acid/
3.	omega 3 fatty acid/
4.	unsaturated fatty acid/ or docosahexaenoic acid/ or icosapentaenoic acid/ or icosapentaenoic acid ethyl ester/ or linolenic acid/ or omega 3 fatty acid ester/
5.	(fish adj3 oil*).ti,ab.
6.	(omega 3 or omega-3).ti,ab.
7.	((n3 or n 3 or n-3) adj3 ((fatty adj3 Acid*) or PUFA*)).ti,ab.
8.	((docosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid*).ti,ab.
9.	(linolenate or omacor or maxepa).ti,ab.
10.	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA* or fatty acid*)).ti,ab.
11.	or/1-10

Cochrane search terms

1	MeSH descriptor Fish Oils explode all trees
2	MeSH descriptor Fatty Acids, Unsaturated, this term only
3	MeSH descriptor Fatty Acids, Omega-3 explode all trees
4	MeSH descriptor Dietary Fats, Unsaturated, this term only

5	(fish near/3 oil*):ti,ab
6	((n-3 or n3 or "n 3") near/3 (PUFA* or "fatty acid" or "fatty acids" or polyunsaturat*)):ti,ab
7	(linolenate or "omega 3" or omega-3 or omacor or maxepa):ti,ab
8	((DHA or ALA or EPA) and (omega or PUFA* or "fatty acid" or "fatty acids")):ti,ab
9	((doxosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or "alpha linolenic" or alpha-linolenic) next acid):ti,ab
10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

F.3.6 Risk tools

Q a) Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults without established CVD (primary prevention)?

b) Which risk assessment tools are the most accurate for predicting the risk of CVD events in adults with diabetes and without established CVD (primary prevention)?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD With additional lines	Risk tools including: QRISK 2 Framingham Age alone		The following filters were used in Medline and Embase only: SR and RCT	See Table 1
CVD With additional lines	Risk tools including: QRISK 2 UKPDS Risk Engine Age alone		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1.	(Qrisk* or QDiabetes* or JBS3 or ClinRisk*).ti,ab.
2.	(Framingham adj2 (risk* or score* or algorithm* or prediction or calculator)).ti,ab.
3.	FRS.ti,ab.
4.	(SCORE adj3 chart*).ti,ab.
5.	(SCORE adj risk).ti,ab.
6.	(SCORE adj3 (10 y* or 10y*)).ti,ab.
7.	(systematic coronary risk evaluation or risk chart* or HeartScore*).ti,ab.
8.	(SCORE adj3 CVD adj3 risk).ti,ab.
9.	ASSIGN.ti,ab.
10.	((Scottish Intercollegiate Guidelines Network or SIGN) adj3 (risk or score)).ti,ab.
11.	(UKPDS adj3 (Risk* or score* or Engine or calculat*)).ti,ab.
12.	or/1-11
13.	framingham.ti,ab,in.
14.	((CVD or CHD) adj risk).ti,ab.
15.	13 and 14
16.	12 or 15

Embase search terms

1	Qrisk score/
2	Framingham risk score/
3	(Qrisk$ or QDiabetes$ or JBS3 or ClinRisk*).ti,ab.
4	(Framingham adj2 (risk$ or score$ or algorithm$ or prediction or calculator)).ti,ab.
5	FRS.ti,ab.
6	(SCORE adj3 chart*).ti,ab.
7	(SCORE adj risk).ti,ab.
8	(SCORE adj3 (10 y* or 10y*)).ti,ab.
9	(systematic coronary risk evaluation or risk chart$ or HeartScore$).ti,ab.
10	(SCORE adj3 CVD adj3 risk).ti,ab.
11	ASSIGN.ti,ab.
12	((Scottish Intercollegiate Guidelines Network or SIGN) adj3 (risk or score)).ti,ab.
13	(UKPDS adj3 (Risk$ or score$ or Engine or calculat$)).ti,ab.
14	or/1-13
15	Framingham.ti,ab,in.
16	((CVD or CHD) adj risk).ti,ab.
17	15 and 16
18	14 or 17

Cochrane search terms

1	(Qrisk* or QDiabetes* or JBS3 or ClinRisk*):ti,ab,kw
2	(Framingham near/2 (risk* or score* or algorithm* or prediction or calculator)):ti,ab,kw
3	FRS:ti,ab,kw
4	(SCORE near/3 chart*):ti,ab,kw
5	(SCORE near risk):ti,ab,kw
6	(SCORE near/3 (10 y* or 10y*)):ti,ab,kw
7	(systematic coronary risk evaluation or risk chart* or HeartScore*):ti,ab,kw
8	(SCORE near/3 CVD near/3 risk):ti,ab,kw
9	(ASSIGN near/3 (risk* or scor* or calculat* or CVD or cardiovascular)):ti,ab,kw
10	((Scottish Intercollegiate Guidelines Network or SIGN) near/3 (risk or score)):ti,ab,kw
11	(UKPDS near/3 (Risk* or score* or Engine or calculat*)):ti,ab,kw
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
13	Framingham:ti,ab,kw
14	((CVD or CHD) near/1 risk):ti,ab,kw
15	13 and 14
16	12 or 15

F.3.7 Stanols and sterols

Q. What is the clinical and cost effectiveness of foods enriched with phytosterols (plant stanols and sterols) or phytosterol supplements versus placebo for adults without established CVD?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD With additional lines	Stanols and sterols		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1	sterols/ or exp phytosterols/
2	(stanol* or sterol* or plant steroid or plant steroids or phytosterol* or phytasterol* or sitosterol* or campesterol* or campestanol* or stigmasterol* or sitostanol* or benecol*).ti,ab.
3	1 or 2

Embase search terms

1	(stanol* or sterol* or plant steroid or plant steroids or stigmasterol or phytasterol* or phytosterol* or sitosterol* or campesterol* or sitostanol* or campestanol* or benecol*).ti,ab.
2	sterol/ or campestanol/ or campesterol/ or phytosterol/ or sitostanol/ or sitosterol/
3	1 or 2

Cochrane search terms

1	MeSH descriptor: [Sterols] this term only
2	MeSH descriptor: [Phytosterols] explode all trees
3	(stanol* or sterol* or phytosterol* or phytasterol* or stigmasterol* or campesterol* or campestanol* or benecol or sitosterol* or sitostanol* or "plant steroid" or plant steroids):ti,ab
4	#1 or #2 or #3

AMED search terms

1	sterols/
2	(stanol* or sterol* or plant steroid or plant steroid* or phytasterol* or phytosterol* or sitosterol* or campesterol* or sitostanol* or campestanol* or stigmasterol* or benecol*).ti,ab.
3	1 or 2

F.3.8 Statins adherence

Q. What is the clinical and cost effectiveness of interventions that improve adherence to statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
No population used	Coenzyme Q_{10} Vitamin D		The following filters were used in Medline and Embase only: SR, RCT, OBS	See Table 1

Medline search terms

1.	exp hydroxymethylglutaryl-coa reductase inhibitors/
2.	statin$.ti,ab.
3.	((hydroxymethylglutaryl-coa or hmg-coa) adj3 (reductase or inhibitors)).ti,ab.
4.	exp simvastatin/
5.	(simvastatin* or zocor).ti,ab.
6.	(atorvastatin* or lipitor).ti,ab.
7.	(rosuvastatin* or crestor).ti,ab.
8.	exp pravastatin/
9.	(pravastatin* or lipostat).ti,ab.
10.	(fluvastatin* or lescol).ti,ab.
11.	or/1-10
12.	ubiquinone/
13.	coenzyme q$.ti,ab.
14.	ubiquinone.ti,ab.
15.	(ubidecarenone or q-ter or bio-quinone or coq$ or ubisemiquinone).ti,ab.
16.	or/12-15
17.	exp vitamin d/
18.	(vitamin adj (d or d2 or d3 or d4 or d5)).ti,ab.
19.	(dihydrotachysterol$ or maxacalcitol or calciferol or calcifediol or doxercalciferol or cholecalciferol or ercalcidiol or hectorol or sitocalcalciferol or paracalcin).ti,ab.
20.	(paracalcitol or zemplar or ergocalciferol or alfacalcidol or one-alpha or calcitriol or rocaltrol or calcijex or oxacalcitriol or falecalcitriol or fluorocalcitriol).ti,ab.
21.	(dihdroxyvitamin$ or hydroxyvitamin$ or hydroxycalciferol or dihydroxycalciferol or hydroxyergocalciferol or dihydroxyergocalciferol or hydroxycholecalciferol or dihydroxycholecalciferol).ti,ab.
22.	or/17-21
23.	medication adherence/
24.	(statin$ adj3 (adher$ or non-adher$)).ti,ab.
25.	16 or 22 or 23 or 24
26.	11 and 25

Embase search terms

1.	exp *hydroxymethylglutaryl-coa reductase inhibitor/
2.	((hydroxymethylglutaryl-coa or hmg-coa) adj3 (reductase or inhibitors)).ti,ab.
3.	statin$.ti,ab.
4.	exp simvastatin/
5.	(simvastatin* or zocor).ti,ab.
6.	(atorvastatin* or lipitor).ti,ab.
7.	(rosuvastatin* or crestor).ti,ab.
8.	exp pravastatin/
9.	(pravastatin* or lipostat).ti,ab.
10.	(fluvastatin* or lescol).ti,ab.
11.	exp atorvastatin/ or exp rosuvastatin/
12.	or/1-11
13.	ubiquinone/
14.	ubiquinone derivative/
15.	coenzyme q$.ti,ab.
16.	ubiquinone.ti,ab.
17.	(ubidecarenone or q-ter or bio-quinone or coq$ or ubisemiquinone).ti,ab.
18.	or/13-17
19.	exp vitamin d/
20.	(vitamin adj (d or d2 or d3 or d4 or d5)).ti,ab.
21.	(dihydrotachysterol$ or maxacalcitol or calciferol or calcifediol or doxercalciferol or cholecalciferol or ercalcidiol or hectorol or sitocalcalciferol or paracalcin).ti,ab.
22.	(paracalcitol or zemplar or ergocalciferol or alfacalcidol or one-alpha or calcitriol or rocaltrol or calcijex or oxacalcitriol or falecalcitriol or fluorocalcitriol).ti,ab.
23.	(dihdroxyvitamin$ or hydroxyvitamin$ or hydroxycalciferol or dihydroxycalciferol or hydroxyergocalciferol or dihydroxyergocalciferol or hydroxycholecalciferol or dihydroxycholecalciferol).ti,ab.
24.	or/19-23
25.	(statin$ adj3 (adher$ or non-adher$)).ti,ab.
26.	18 or 24 or 25
27.	12 and 26

Cochrane search terms

1	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
2	((Hydroxymethylglutaryl-CoA or HMG-CoA) near/3 (reductase or inhibitors)):ti,ab
3	MeSH descriptor: [Simvastatin] this term only
4	(statin* or simvastatin* or zocor):ti,ab
5	(atorvastatin* or lipitor):ti,ab
6	(rosuvastatin* or crestor):ti,ab
7	mesh descriptor: [pravastatin] this term only
8	(pravastatin* or lipostat):ti,ab
9	(fluvastatin* or lescol):ti,ab
10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
11	MeSH descriptor: [Ubiquinone] this term only
12	("coenzyme Q10"):ti,ab
13	("coenzyme Q" or "coenzyme Q(10)"):ti,ab

14	(ubiquinone or ubidecarenone or Q-ter or bio-quinone or coQ or coQ10 or ubisemiquinone):ti,ab
15	MeSH descriptor: [Vitamin D] explode all trees
16	(vitamin next/1 (D or D2 or D3 or D4 or D5)):ti,ab
17	MeSH descriptor: [Medication Adherence] this term only
18	((adher* or non-adher* or nonadher*) near/3 statin*) .ti,ab
19	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20	#10 and #19

F.3.9 Statins adverse events

Q. Who is at risk of adverse effects from statin treatment? (Are some subgroups at different risk of adverse events?)

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
No population used	Simvastatin Atorvastatin Rosuvastatin Pravastatin Fluvastatin		The following filters were used in Medline and Embase only: SR, RCT, OBS and RISK	See Table 1

Medline search terms

1.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2.	statin$.ti,ab.
3.	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti,ab.
4.	exp *simvastatin/
5.	(simvastatin* or zocor).ti,ab.
6.	(atorvastatin* or lipitor).ti,ab.
7.	(rosuvastatin* or crestor).ti,ab.
8.	exp *pravastatin/
9.	(pravastatin* or lipostat).ti,ab.
10.	(fluvastatin* or lescol).ti,ab.
11.	or/1-10
12.	diabetes mellitus/ci or exp diabetes mellitus, type 2/ci
13.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/ae
14.	exp *pravastatin/ae or exp *simvastatin/ae
15.	rhabdomyolysis/ci [chemically induced]
16.	musculoskeletal pain/ci
17.	muscular diseases/ci [chemically induced]
18.	cataract/ci [chemically induced]
19.	drug-induced liver injury/
20.	acute kidney injury/ci [chemically induced]
21.	muscular disorders, atrophic/ci [chemically induced]
22.	muscular atrophy/ci [chemically induced]
23.	muscle weakness/ci [chemically induced]

24.	polyneuropathies/ci [chemically induced]
25.	fatigue/ci
26.	(statin$ adj2 risk$).ti.
27.	((myalgia$ or myopath$ or fatigue or tiredness or polyneuropath$ or neuropath$ or rhabdomyolysis) adj10 statin$).ti,ab.
28.	((muscle$ or muscular or musculoskeletal) adj2 (pain or tenderness or weakness) adj10 statin$).ti,ab.
29.	(nerve damage adj10 statin$).ti,ab.
30.	((incident or new onset) adj2 diabetes adj10 statin$).ti,ab.
31.	((hepatic or liver or renal or kidney) adj2 (failure or dysfunction or problem$) adj10 statin$).ti,ab.
32.	((raised or elevat$) adj3 (liver enzymes or hepatic enzymes) adj10 statin$).ti,ab.
33.	((side or adverse or unintended) adj2 (event$ or effect$) adj3 statin$).ti,ab.
34.	or/12-33
35.	11 and 34

Embase search terms

1.	*Hydroxymethylglutaryl-CoA Reductase Inhibitor/
2.	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti.
3.	statin$.ti.
4.	exp *simvastatin/
5.	(simvastatin* or zocor).ti.
6.	(atorvastatin* or lipitor).ti.
7.	(rosuvastatin* or crestor).ti.
8.	exp *pravastatin/
9.	(pravastatin* or lipostat).ti.
10.	(fluvastatin* or lescol).ti.
11.	exp *atorvastatin/ or exp *rosuvastatin/
12.	or/1-11
13.	*hydroxymethylglutaryl-coa reductase inhibitor/ae
14.	*rhabdomyolysis/si [side effect]
15.	*diabetes mellitus/si [side effect]
16.	*non insulin dependent diabetes mellitus/si [side effect]
17.	*musculoskeletal pain/si [side effect]
18.	*muscle weakness/si or *fatigue/si
19.	*liver dysfunction/si [side effect]
20.	*toxic hepatitis/si
21.	*myalgia/si [side effect]
22.	*myopathy/si [side effect]
23.	*muscle disease/si [side effect]
24.	*cataract/si [side effect]
25.	*acute kidney failure/si [side effect]
26.	*muscle atrophy/si [side effect]
27.	*polyneuropathy/si [side effect]
28.	*drug induced disease/ and statin$.ti,ab.
29.	(statin$ adj2 risk$).ti.

30.	((myalgia$ or myopath$ or fatigue or tiredness or polyneuropath$ or neuropath$ or rhabdomyolysis) adj10 statin$).ti,ab.
31.	((muscle$ or muscular or musculoskeletal) adj2 (pain or tenderness or weakness) adj10 statin$).ti,ab.
32.	(nerve damage adj10 statin$).ti,ab.
33.	((incident or new onset) adj2 diabetes adj10 statin$).ti,ab.
34.	((hepatic or liver or renal or kidney) adj2 (failure or dysfunction or problem$) adj10 statin$).ti,ab.
35.	((raised or elevat$) adj3 (liver enzymes or hepatic enzymes) adj10 statin$).ti,ab.
36.	((side or adverse or unintended) adj2 (event$ or effect$) adj3 (pravastatin or simvastatin or fluvastatin or atorvastatin or zocor or lipitor or rosuvastatin or crestor or lipostat or lescol or statin$)).ti,ab.
37.	or/13-36
38.	12 and 37

Cochrane search terms

1	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only
2	((Hydroxymethylglutaryl-CoA or HMG-CoA) near/3 (reductase or inhibitors)):ti
3	MeSH descriptor: [Simvastatin] explode all trees
4	statin*:ti
5	(simvastatin* or zocor):ti
6	(atorvastatin* or lipitor):ti
7	(rosuvastatin* or crestor):ti
8	MeSH descriptor: [Pravastatin] explode all trees
9	(pravastatin* or lipostat):ti
10	(fluvastatin* or lescol):ti
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MeSH descriptor: [Diabetes Mellitus] this term only and with qualifiers: [Chemically induced - CI]
13	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees and with qualifiers: [Chemically induced - CI]
14	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only and with qualifiers: [Adverse effects - AE]
15	MeSH descriptor: [Rhabdomyolysis] this term only and with qualifiers: [Chemically induced - CI]
16	MeSH descriptor: [Muscular Diseases] this term only and with qualifiers: [Chemically induced - CI]
17	MeSH descriptor: [Cataract] this term only and with qualifiers: [Chemically induced - CI]
18	MeSH descriptor: [Drug-Induced Liver Injury] this term only
19	MeSH descriptor: [Acute Kidney Injury] this term only and with qualifiers: [Chemically induced - CI]
20	MeSH descriptor: [Muscular Atrophy] this term only and with qualifiers: [Chemically induced - CI]
21	MeSH descriptor: [Muscle Weakness] this term only and with qualifiers: [Chemically induced - CI]
22	MeSH descriptor: [Polyneuropathies] this term only and with qualifiers: [Chemically induced - CI]
23	MeSH descriptor: [Fatigue] this term only and with qualifiers: [Chemically induced - CI]
24	(statin near/2 risk*):ti

25	((myalgia* or myopath* or fatigue or tiredness or polyneuropath* or neuropath* or rhabdomyolysis) near/10 statin*):ti,ab
26	((muscle* or muscular or musculoskeletal) near/2 (pain or tenderness or weakness) near/10 statin*):ti,ab
27	(((incident or new-onset) next/1 diabetes) near/10 statin*):ti,ab
28	((hepatic or liver or renal or kidney) near/2 (failure or dysfunction or problem*) near/10 statin*):ti,ab
29	((raised or elevat*) near/3 ("liver enzymes" or "hepatic enzymes") near/10 statin*) .ti,ab
30	((side or adverse or unintended) near/2 (event* or effect*) near/3 (pravastatin or atorvastatin or rosuvastatin or fluvastatin or lipitor or crestor or simvastatin or zocor or lescol or lipostat or statin*)) .ti,ab
31	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
32	#11 and #31

F.3.10 Statins efficacy

Q. For adults without established CVD (primary prevention) and with established CVD (secondary prevention) what is the clinical and cost effectiveness of statin therapy?

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD With additional lines	Simvastatin Atorvastatin Rosuvastatin Pravastatin Fluvastatin		The following filters were used in Medline and Embase only: SR and RCT	See Table 1

Medline search terms

1	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2	statin*.ti,ab.
3	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti,ab.
4	exp *simvastatin/
5	(simvastatin* or zocor).ti,ab.
6	(atorvastatin* or lipitor).ti,ab.
7	(rosuvastatin* or crestor).ti,ab.
8	exp *pravastatin/
9	(pravastatin* or lipostat).ti,ab.
10	(fluvastatin* or lescol).ti,ab.
11	or/1-10

Embase search terms

1	*Hydroxymethylglutaryl-CoA Reductase Inhibitor/
2	((Hydroxymethylglutaryl-CoA or HMG-CoA) adj3 (reductase or inhibitors)).ti,ab.
3	statin*.ti,ab.
4	exp *simvastatin/
5	(simvastatin* or zocor).ti,ab.

6	(atorvastatin* or lipitor).ti,ab.
7	(rosuvastatin* or crestor).ti,ab.
8	exp *pravastatin/
9	(pravastatin* or lipostat).ti,ab.
10	(fluvastatin* or lescol).ti,ab.
11	exp *atorvastatin/ or exp *rosuvastatin/
12	or/1-11

Cochrane search terms

1	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only
2	((Hydroxymethylglutaryl-CoA or HMG-CoA) near/3 (reductase or inhibitors)):ti,ab
3	MeSH descriptor: [Simvastatin] this term only
4	(simvastatin* or zocor):ti,ab
5	(atorvastatin* or lipitor):ti,ab
6	(rosuvastatin* or crestor):ti,ab
7	mesh descriptor: [pravastatin] this term only
8	(pravastatin* or lipostat):ti,ab
9	(fluvastatin* or lescol):ti,ab
10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

Economics search

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

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

Population	Intervention or exposure	Comparison	Study filter used	Date parameters
CVD or hyperlipidaemia or stanols or sterols anion exchange resins omega-3 nicotinic acids fibrates			The following filters were used in Medline and Embase only: HE	Medline: Oct 2012 – 20/11/13 Embase: Week 40 - 20/11/13

Medline search terms

1	hyperlipidemias/ or hypercholesterolemia/ or dyslipidemias/
2	(dyslipid?emi$ or hyperlipid?emi$ or hypercholesterol?emi$ or hyperlip?emi$).ti,ab.
3	(hypolipid?emic or hypocholesterol?emic).ti,ab.
4	((lipid$ or cholesterol) adj3 (disorder$ or abnormal$ or level$ or modif$)).ti,ab.
5	((high* or raised or elevat* or increas*) adj3 (cholesterol or lipid$)).ti,ab.
6	((reduced or reduction or reducing or low* or decreas*) adj3 (cholesterol or lipid*)).ti,ab.
7	or/1-6
8	Cardiovascular Diseases/
9	Heart diseases/
10	Myocardial Ischemia/

11	exp Angina Pectoris/
12	Coronary Disease/
13	Coronary Artery Disease/
14	exp Coronary Stenosis/
15	Myocardial Infarction/
16	exp Heart Failure/
17	arrhythmias, cardiac/ or atrial fibrillation/
18	Vascular Diseases/
19	hypertension/
20	Atherosclerosis/
21	Peripheral Arterial Disease/
22	Peripheral Vascular Diseases/
23	Arteriosclerosis/
24	Cerebrovascular Disorders/
25	exp Stroke/
26	exp brain ischemia/
27	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
28	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
29	(MI or myocardial infarct$).ti,ab.
30	(CVD or CHD or CAD or PAD or CVA).ti,ab.
31	(hypertension or hypertensive$).ti,ab.
32	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
33	(atheroscleros$ or arterioscleros$).ti,ab.
34	(cerebrovascular accident$ or stroke$).ti,ab.
35	(ACS or angina or acute coronary syndrome$).ti,ab.
36	(AF or atrial fibrillation).ti,ab.
37	((chronic or congestive) adj2 heart failure).ti,ab.
38	(heart or coronary or cardio$ or cardiac$ or atherosclero$ or arteriosclero$ or ischemi$ or ischaemi$ or myocardi$ or atrial$ or infarct$ or vascular or stenos$ or hypertens$ or cerebrovascular).ti,ab.
39	or/8-38
40	sterols/ or exp phytosterols/
41	(stanol$ or sterol$ or plant steroid or plant steroids or phytosterol$ or phytasterol$ or sitosterol$ or campesterol$ or campestanol$ or stigmasterol$ or sitostanol$ or benecol$).ti,ab.
42	40 or 41
43	exp Anion Exchange Resins/
44	((anion exchange or anionic exchange) adj2 resin$).ti,ab.
45	((anion or anionic) adj2 exchanger$).ti,ab.
46	(cholestyramin$ or colestyramin$ or colestimide or cholybar or colextran or colestilan or cholestagel or cholestipol or colestipol or colestid or questran$ or quantalan$ or cuemid$ or colesevelam).ti,ab.
47	(bile acid adj3 (sequestrant$ or sequestering agent$ or resin$)).ti,ab.
48	or/43-47
49	exp Fish Oils/

50	fatty acids, unsaturated/ or exp fatty acids, omega-3/
51	Dietary Fats, Unsaturated/
52	(fish adj3 oil$).ti,ab.
53	(omega 3 or omega-3).ti,ab.
54	((n 3 or n3 or n-3) adj3 ((fatty adj3 acid$) or PUFA$)).ti,ab.
55	((docosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid$).ti,ab.
56	(linolenate or maxepa or omacor).ti,ab.
57	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA* or fatty acid$)).ti,ab.
58	or/49-57
59	Nicotinic Acids/ or niacin/
60	Nicotinic.ti,ab.
61	niacin.ti,ab.
62	(nicotinate$ or acipimox or acipemox).ti,ab.
63	(olbetam or niaspan or tredaptive).ti,ab.
64	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.
65	or/59-64
66	exp Fibric Acids/
67	(fibrate$ or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modalim or ciprofibrate).ti,ab.
68	((fibric or fenofibric or clofibric) adj2 acid$).ti,ab.
69	or/66-68
70	7 or 38 or 42 or 48 or 58 or 65 or 69

Embase search terms

1	*hyperlipidemia/
2	*hypercholesterolemia/
3	(dyslipid?emi$ or hyperlipid?emi$ or hypercholesterol?emi$ or hyperlip?emi$).ti,ab.
4	(hypolipid?emic or hypocholesterol?emic).ti,ab.
5	((lipid$ or cholesterol) adj3 (disorder$ or abnormal$ or level$ or modif$)).ti,ab.
6	((high* or raised or elevat* or increas*) adj3 (cholesterol or lipid$)).ti,ab.
7	((reduced or reduction or reducing or low* or decreas*) adj3 (cholesterol or lipid*)).ti,ab.
8	or/1-7
9	*cardiovascular disease/
10	*coronary artery disease/
11	*vascular disease/
12	*coronary artery atherosclerosis/
13	*peripheral vascular disease/
14	*peripheral occlusive artery disease/
15	*arteriosclerosis/
16	*ischemic heart disease/
17	exp *Stroke/ or *stroke patient/
18	*coronary artery obstruction/
19	*hypertension/
20	*heart disease/
21	*heart arrhythmia/

22	*heart fibrillation/ or *heart atrium fibrillation/
23	*heart failure/ or exp *congestive heart failure/
24	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
25	*cerebrovascular disease/
26	*cerebrovascular accident/
27	exp *brain ischemia/
28	exp *heart arrest/ or *heart death/
29	*brain infarction/
30	*atherosclerosis/
31	exp *cardiovascular risk/
32	((cardiovascular or cardio-vascular or cardio vascular) adj3 (event$ or disease$ or disorder$ or risk$ or benefit$)).ti,ab.
33	((coronary or peripheral vascular or heart or peripheral arter$) adj3 (disease$ or event$ or disorder$ or risk$ or benefit$)).ti,ab.
34	(MI or myocardial infarct$).ti,ab.
35	((heart or cardiopulmonary or cardiac) adj3 (death$ or arrest$ or attack$)).ti,ab.
36	(CVD or CHD or CAD or PAD or CVA).ti,ab.
37	(hypertension or hypertensive$).ti,ab.
38	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
39	(atheroscleros$ or arterioscleros$).ti,ab.
40	(cerebrovascular accident$ or stroke$).ti,ab.
41	(ACS or angina or acute coronary syndrome$).ti,ab.
42	(AF or atrial fibrillation).ti,ab.
43	((chronic or congestive) adj2 heart failure).ti,ab.
44	(heart or coronary or cardio$ or cardiac$ or atherosclero$ or arteriosclero$ or ischemi$ or ischaemi$ or myocardi$ or atrial$ or infarct$ or vascular or stenos$ or hypertens$ or cerebrovascular).ti,ab.
45	or/9-44
46	(stanol$ or sterol$ or plant steroid or plant steroids or stigmasterol or phytasterol$ or phytosterol$ or sitosterol$ or campesterol$ or sitostanol$ or campestanol$ or benecol$).ti,ab.
47	sterol/ or campestanol/ or campesterol/ or phytosterol/ or sitostanol/ or sitosterol/
48	46 or 47
49	fish oil/
50	polyunsaturated fatty acid/
51	omega 3 fatty acid/
52	unsaturated fatty acid/ or docosahexaenoic acid/ or icosapentaenoic acid/ or icosapentaenoic acid ethyl ester/ or linolenic acid/ or omega 3 fatty acid ester/
53	(fish adj3 oil$).ti,ab.
54	(omega 3 or omega-3).ti,ab.
55	((n3 or n 3 or n-3) adj3 ((fatty adj3 Acid$) or PUFA$)).ti,ab.
56	((docosahexaenoic or docosahexenoic or eicosapentaeonic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha linolenic) adj2 acid$).ti,ab.
57	(linolenate or omacor or maxepa).ti,ab.
58	((DHA or ALA or EPA) and (omega 3 or omega-3 or PUFA$ or fatty acid$)).ti,ab.
59	or/50-58
60	exp *fibric acid derivative/
61	((fibric or fenofibric or clofibric) adj2 acid$).ti,ab.

62	(fibrate$ or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modalim or ciprofibrate).ti,ab.
63	60 or 61 or 62
64	*nicotinic acid/ or *laropiprant plus nicotinic acid/ or *acipimox/
65	nicotinic.ti,ab.
66	(niacin or nicotinate$ or acipimox or acipemox or olbetam or niaspan or tredaptive).ti,ab.
67	((3 pyridinecarboxylic or 3-pyridinecarboxylic) adj3 acid).ti,ab.
68	or/64-67
69	exp *anion exchange resin/
70	exp *bile acid sequestrant/
71	*colestilan/ or *colestipol/ or *colestyramine/ or *colesevelam/ or *diethylaminoethyldextran/
72	((anion exchange or anionic exchange) adj2 resin$).ti,ab.
73	((anion or anionic) adj2 exchanger$).ti,ab.
74	(cholestyramin$ or colestyramin$ or colestimide or cholybar or colextran or colestilan or cholestagel or colestipol or cholestipol or colestid or questran$ or quantalan$ or cuemid$ or colesevelam).ti,ab.
75	(bile acid adj3 (sequestrant$ or sequestering agent$ or resin$)).ti,ab.
76	or/69-75
77	8 or 45 or 48 or 59 or 63 or 68 or 76

CRD search terms

1	MeSH DESCRIPTOR Hyperlipidemias EXPLODE ALL TREES IN NHSEED,HTA
2	MeSH DESCRIPTOR Hyperlipidemias EXPLODE ALL TREES WITH QUALIFIER hypercholesterolemia IN NHSEED,HTA
3	MeSH DESCRIPTOR Hyperlipidemias EXPLODE ALL TREES WITH QUALIFIER dyslipidemias IN NHSEED,HTA
4	(dyslipidaemi*):TI OR (dyslipidemi*):TI OR (hyperlipidemi*):TI OR (hyperlipidaemi*):TI IN NHSEED, HTA
5	(hypercholesterolemi*):TI OR (hypercholesterolaemi*):TI OR (hyperlipaemi*):TI OR (hyperlipemi*):TI IN NHSEED, HTA
6	(hypolipidaemic):TI OR (hypolipidemic):TI OR (hypocholesterolaemic):TI OR (hypocholesterolemic):TI IN NHSEED, HTA
7	(hypolipidaemic):TI OR (hypolipidemic):TI OR (hypocholesterolaemic):TI OR (hypocholesterolemic):TI IN NHSEED, HTA
8	(lipid*):TI OR (cholesterol):TI IN NHSEED, HTA
9	(disorder*):TI OR (abnormal*):TI OR (level*):TI OR (modif*):TI OR (high*):TI IN NHSEED, HTA
10	(raised):TI OR (elevat*):TI OR (increas*):TI OR (reduced):TI OR (reduction):TI IN NHSEED, HTA
11	(reducing):TI OR (low*):TI OR (decreas*):TI IN NHSEED, HTA
12	#9 OR #10 OR #11
13	#8 AND #12
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #13
15	MeSH DESCRIPTOR cardiovascular diseases
16	MeSH DESCRIPTOR coronary disease
17	MeSH DESCRIPTOR vascular diseases
18	MeSH DESCRIPTOR coronary artery disease
19	MeSH DESCRIPTOR atherosclerosis
20	MeSH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES

21	MeSH DESCRIPTOR arteriosclerosis
22	MeSH DESCRIPTOR heart diseases
23	MeSH DESCRIPTOR stroke EXPLODE ALL TREES
24	(CVD OR CHD OR CAD OR PAD OR CVA):TI
25	(((cardiovascular OR cardio-vascular) NEAR3 (event* OR disease*))):TI OR (((coronary OR peripheral vascular or heart or peripheral arterial) NEAR3 (event* OR disease*))):TI OR (atheroscleros* OR stroke* OR cerebrovascular accident* OR arterioscleros*):TI
26	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	MeSH DESCRIPTOR secondary prevention
28	MeSH DESCRIPTOR primary prevention
29	MeSH DESCRIPTOR risk
30	MeSH DESCRIPTOR risk factors
31	MeSH DESCRIPTOR risk assessment
32	(((cardio* OR cardiac OR stroke or coronary) NEAR3 (risk OR prevention))):TI OR (((risk OR prevent*) NEAR3 (coronary OR cardio* OR stroke* OR cardiac))):TI
33	#27 OR #28 OR #29 OR #30 OR #31 OR #32
34	(((high OR raised OR elevated) NEAR2 cholesterol)):TI OR ((lipid* NEAR3 (disorder* OR abnormal*))):TI
35	(dyslipidemia* or hyperlipidemia* or hyperlipemia* OR hypercholesterolemia)
36	MeSH DESCRIPTOR hypercholesterolemia
37	MeSH DESCRIPTOR Hyperlipidemias
38	#34 OR #35 OR #36 OR #37
39	#26 AND #33
40	#38 OR #39
41	MeSH DESCRIPTOR cardiovascular diseases
42	MeSH DESCRIPTOR heart diseases
43	MeSH DESCRIPTOR myocardial ischemia
44	MeSH DESCRIPTOR angina pectoris EXPLODE ALL TREES
45	MeSH DESCRIPTOR coronary disease
46	MeSH DESCRIPTOR coronary artery disease
47	MeSH DESCRIPTOR coronary stenosis
48	MeSH DESCRIPTOR myocardial infarction
49	MeSH DESCRIPTOR heart failure EXPLODE ALL TREES
50	MeSH DESCRIPTOR arrhythmias, cardiac
51	MeSH DESCRIPTOR vascular diseases
52	MeSH DESCRIPTOR atrial fibrillation
53	MeSH DESCRIPTOR hypertension
54	MeSH DESCRIPTOR atherosclerosis EXPLODE ALL TREES
55	MeSH DESCRIPTOR peripheral vascular diseases
56	MeSH DESCRIPTOR arteriosclerosis
57	MeSH DESCRIPTOR cerebrovascular disorders
58	MeSH DESCRIPTOR stroke EXPLODE ALL TREES
59	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES
60	MeSH DESCRIPTOR heart arrest EXPLODE ALL TREES
61	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60

62	(CVD or CVA or CHD or PAD or CAD or MI or ACS or AF)
63	(((high or raised or elevated) adj3 ("blood pressure" or BP)))
64	((peripheral adj2 arter*))
65	((stroke* or angina or atrial or heart or coronary or cardio* or cardiac* or athersclero* or arteriosclero* or ischemi* or ischaemi* or myocardi* or infarct* or vascular* or stenos* or hypertens* or cerebrovascular))
66	#61 OR #62 OR #63 OR #64 OR #65
67	MeSH DESCRIPTOR sterols
68	MeSH DESCRIPTOR phytosterols EXPLODE ALL TREES
69	((stanol* or sterol* or phytosterol* or phytasterol* or stigmasterol* or campesterol* or campestanol* or benecol or sitosterol* or sitostanol* or "plant steroid" or "plant steroids"))
70	MeSH DESCRIPTOR fibric acids EXPLODE ALL TREES
71	(((fibric or clofibric or fenofibric) adj2 acid*))
72	((fibrate* or bezafibrate or clofibrate or fenofibrate or lopid or gemfibrozil or bezalip or tricor or fibricor or lipantil or supralip or modim or ciprofibrate))
73	MeSH DESCRIPTOR nicotinic acids
74	MeSH DESCRIPTOR niacin
75	((nicontinic or niacin or nicotinate* or niaspan or olbetam or tredaptive or acipimox or acipemox))
76	MeSH DESCRIPTOR anion exchange resins EXPLODE ALL TREES
77	(("anion exchange" or "anionic exchange") adj2 resin*)
78	((anion or anionic) adj2 exchanger*)
79	((cholestyramin* or colestyramin* or colestimide or colestid or cholyber or colextran or colestilan or cholestagel or colestipol or cholestipol or questran or quantalan or cuemid or colesevelam))
80	("bile acid") adj3 (sequestrant* or "sequestering agent" or "sequestering agents" or resin*)
81	MeSH DESCRIPTOR fish oils EXPLODE ALL TREES
82	MeSH DESCRIPTOR fatty acids, unsaturated
83	MeSH DESCRIPTOR fatty acids, omega-3 EXPLODE ALL TREES
84	MeSH DESCRIPTOR dietary fats, unsaturated
85	(fish adj3 oil*)
86	(linolenate*)
87	(((omega-3 or "omega 3" or n-3 or "n 3" or n3) adj3 (PUFA or PUFAS or "fatty acid" or "fatty acids")))
88	(((DHA or ALA or EPA) adj6 (omega or PUFA* or "fatty acid" or "fatty acids")))
89	(((doxosahexaenoic or docosahexenoic or eicosapentaenoic or eicosapentanoic or icosapentaenoic or timnodonic or linolenic or a-linolenic or alpha-linolenic) adj2 acid))
90	#67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
91	#66 AND #90
92	#40 OR #91
94	#14 OR #40 OR #91

HEED search terms

1	ax=hyperlipidemi* or hyperlipidaemia*
2	ax=hypercholesterolemi* or hypercholesterolaemi*
3	ax=dyslipidemi* or dyslipidaemi*
4	cs=1 or 2 or 3

5	ax=disorder* or abnormal*
6	ax=lipid*
7	cs=5 and 6
8	ax=high or raised or elevated
9	ax=cholesterol
10	cs=8 and 9
11	cs=4 or 7 or 10
12	ax=lipid* or cholesterol
13	ax= disorder* or abnormal* or level* or modif* or high* or raised or elevat* or incres* or reduced or reduction or reducing or low* or decreas*
14	cs=12 and 13
15	cs=11 or 14

Appendix G: Clinical evidence tables

G.1 Risk assessment tools

Table 2: Anderson 1991[91]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome /target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Anderson 1991. An Updated Coronary Risk Profile. A Statement for Health Professionals. Circulation. 1991; 83: 356-362. Funding: not stated	Cohort study. Original Framingham and Framingham Offspring Cohorts. Derivation of the Framingham-Anderson tool. USA	n=2590 Inclusion criteria: age 30-74 years at the time of the baseline examination; measurements available for SBP and DBP, cigarette smoking status, total and HDL cholesterol, and diagnoses (yes or no) of diabetes and ECG-LVH (when information on diabetes or LVH was not available, diagnoses were presumed to be negative);	Baseline examination between 1968 and 1975. **Baseline characteristics: see** Table 4.	Framingham-Anderson. Risk factors included: • Age • Gender • HDL-C • T-C • SBP • Smoking • Diabetes • ECG-LVH	CHD incidence. n=1252 (482 in women)	12 years			Parametric regression model. Worksheet to estimate CHD risk based on systolic blood pressure equation.

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome /target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
		freedom from CVD (stroke, transient ischemia, CHD [includes angina pectoris, coronary insufficiency (unstable angina), myocardial infarction, and sudden death], congestive heart failure, and intermittent claudication) until time of risk factor measurement. Exclusion criteria: History of stroke, transient ischaemia, intermittent claudication, and cancer (other than basal cell carcinomas). Physician assessed definite angina pectoris, myocardial infarction and							

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome /target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
		congestive cardiac failure. Definite electrocardiographic evidence of myocardial infarction and coronary insufficiency. Doubtful electrocardiographic evidence of myocardial infarction.							

Framingham risk equations for coronary heart disease death (B1) and coronary heart disease events (B2) in men over 10 years

- Step 1

For coronary heart disease mortality calculate*

$\mu = 11.2889 - 0.588\times\log(\text{systolic blood pressure}) - 0.1367\times\text{smoking} - 0.3448\times\log(\text{total/high density lipoprotein cholesterol}) - 0.1237\times\text{electrocardiographic left ventricular hypertrophy} - 0.944\times\log(\text{age}) - 0.0474\times\text{diabetes}$

$\sigma = \exp(2.9851 - 0.9142\mu)$ (**B1**)

For coronary heart disease events calculate*

$\mu = 15.5303 - 0.9119\times\log(\text{systolic blood pressure}) - 0.2767\times\text{smoking} - 0.7181\times\log(\text{total/high density lipoprotein cholesterol}) - 0.5865\times\text{electrocardiographic left ventricular hypertrophy} - 1.4792\times\log(\text{age}) - 0.1759\times\text{diabetes}$

$\sigma = \exp(- 0.3155 - 0.2784\times(\mu - 4.4181))$ (**B2**)

- Step 2

For both equations calculate:

$\mu = (\log(10) - \mu)/\sigma$ Length of follow up = 10 years

- Step 3

The predicted probability is then given by:

$p=1 - \exp(-\exp(u))$

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome /target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
**Variables smoking, electrocardiographic left ventricular hypertrophy, and diabetes are set to 1 when present and 0 when absent. Systolic blood pressure measured in mm Hg and age in years.*									

Table 3: Brindle 2003[220]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/ target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Brindle 2003. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ. 2003 November 29; 327(7426): 1267.	Cohort study. The The British regional heart study(1978-80),: prospective study of 7735 men, randomly selected from the age and sex registers	n=6643 men Inclusion criteria: age 40-59 years. Exclusion criteria: Rose angina (definite grade I or II), self-report of doctor diagnosis of: coronary thrombosis, myocardial infarction, heart attack, angina, or stroke.	Patient registered from 27 June 1994 and 30 June 2008. **Baseline characteristics: see** Table 4.	Framingham-Anderson tool	CHD events and mortality n= 183 deaths from CHD n=677 deaths from CHD, any diagnosis of MI or angina	Lost to follow up <1%	30% threshold		
							Sensitivity	16%	
							Specificity	94%	
							15% threshold		
							Sensitivity	75%	
							Specificity	55%	
							30% threshold (after recalibration)		
							Sensitivity	1.8%	
							Specificity	99.6%	
							15% threshold (after recalibration)		
							Sensitivity	37%	
							Specificity	85%	
							Recalibration: divide the calculated score by the amount of over-prediction:		

Funding: the Wellcome Trust	of one general practice in each of 24 towns in the UK. Validation of the Framingham-Anderson tool.	Definite electrocardiographic evidence of myocardial infarction.					1.47	

Table 4: Anderson 1991[91]; Brindle 2003[220]; patients baseline characteristics

Characteristic	Framingham (n=2590) (Anderson 1991)	British regional heart study (n=6643) (Brindle 2003)
Period of baseline data collection	1968-75	1978-80
10 year coronary heart disease mortality (%)	NA	2.8
10 year coronary heart disease event rate (%)	12.4	10.2
Age range (years) at baseline	30-74	40-59
Smoking (%)	40.7	41.9
Diabetes (%)	7.1	1.1
Electrocardiographic evidence of left ventricular hypertrophy (%)	1.1	2.6
Median (95% CI) blood pressure (mm Hg):		
Systolic blood pressure	128 (109 to 168)	143 (115 to 182)
Diastolic blood pressure	82 (69 to 102)	81 (62 to 105)
Median ratio (95% CI) of total to high density lipoprotein cholesterol	4.8 (2.9 to 8.0)	5.5 (3.5 to 8.6)

Table 5: Brindle 2003[220] – QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. CHD events and CHD mortality	Patient enrolment: consecutive. Study Design: retrospective cohort. Validation: adequate Validation. Selection bias overall: low	Imputation: no imputation. Lost to follow up <1% Index test bias overall: low	Analysis method: time to event analysis Length of follow-up: appropriate. Missing outcome data: no missing data. Patient outcome measurement: acceptable. Comments: Data from registers of general practice. Patient outcome bias overall: low	No. of events: ≥100 events Comments: 677 CHD events recorded; data quality poor (GP database) Other bias overall: high	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	High

Table 6: Brunner 2010[237]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Brunner 2010. Do the Joint	Cohort study, (Whitehall II)	n=6868 Baseline Examination between 1991-1993.	Baseline characteristics	Framingham-Wilson	CHD events n=443 (277 developed diabetes only,	Median: 11.3 (2.6) years	Framingham-Wilson, CHD		Adding glycaemic status or fasting glucose did
							AUC	0.70 (0.68-0.73)	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
British Society (JBS2) guidelines on prevention of cardiovascular disease with respect to plasma glucose improve risk stratification in the general population? Prospective cohort study. Diabetic Medicine, 27, 550-555. Funding: Medical Research Council, British Heart	UK	Inclusion criteria: civil servant aged 35-55; no prevalent CHD or diabetes. Exclusion criteria: lack of data for 1 or more risk factors (SBP, T-C, HDL-C, BMI, fasting glucose, smoking status).			50 developed both CHD and diabetes)				not change AUC.

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Foundation, Health and Safety Executive, Department of Health,									

Table 7: Brunner 2010[237]; baseline characteristics

	Men (n=4775)	Women (n=2093)
Age (years)	49.2±5.9	50.1±6.0
BMI (Kg/m^2)	25.1±3.1	25.6±4.7
SBP (mmHg)	122±13	118±14
DBP (mmHg)	81±9	77±9
Current smoking (%)	12.1	16.0
T-C (mmol/l)	6.5±1.1	6.5±1.2
HDL-C (mmol/l)	1.3±0.3	1.7±0.4
LDL-C (mmol/l)	4.4±1.0	4.3±1.1
Fasting glucose (mmol/l)	5.3±0.7	5.1±0.6

Table 8: Brunner 2010[237]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Wilson.	Patient enrolment: Whitehall II cohort.	Imputation: No imputation.	Analysis method adequate	No. of events: >100. Adequate	Population: appropriate to	Low

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
CHD events	Study Design: prospective cohort. Validation: . Selection bias overall: low	Lost to follow up: not stated. Index test bias overall: unclear	Length of follow-up: 11 years. Adequate. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: Patient outcome bias overall: Unclear	Comments: 443 CHD events Other bias overall: Low	review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 9: Chamnan 2010[289]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Chamnan 2010. A simple risk score using routine data for predicting cardiovascu	Cohort study. European Prospective Investigation of Cancer [EPIC]–	n=21,867 (n=9602 men and n=12,265 women). Inclusion criteria: age 40-74; free from diabetes. Exclusion	Patients recruited from general practices in the Norfolk region, England, between 1993 and 1997.	Framingham-D'Agostino (2008) (Cambridge, not extracted)	n=2213 CVD events. (n=1348 men and n=865 women).	11.0 years (median)	Framingham-D'Agostino		.
							AUC	0.77 (0.76-0.78)	
							30% cut-off		
							Sensitivity	41.4 (39.4-43.5)	
							Specificity	87.8 (87.3-88.3)	
							20% cut-off		

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
lar disease in primary care. British J of General Practice, August 2010. Funding: Medical Research Council, Cancer Research UK, British Heart Foundation, European Union, Stroke Association, Wellcome Trust, Research into Ageing, the Academy of Medical Science	Norfolk.	criteria: individuals with CVD at baseline; those with missing values for 1 or more of the variables used to calculate the Framingham risk score.	Baseline characteristics: see Table 10.				Sensitivity	65.7 (63.7-67.7)	
							Specificity	73.6 (73.0-74.2)	
							15% cut-off		
							Sensitivity	79.3 (77.5-81.0)	
							Specificity	61.2 (60.5-61.8)	
							Predicted CVD risk	16.2%	
							Observed CVD risk	10.1%	

Table 10: Chamnan 2010[289]; baseline characteristics

Characteristic	Men did not develop CVD (n=8254)	Men developed CVD (n=1348)	Women did not develop CVD (n=11,400)	Women developed CVD (n=865)
Age, mean (SD), y	57.8 (9.2)	64.1 (8.2)	57.4 (9.1)	66.3 (7.4)
Social Class, No (%)				
Professional	662 (8.1)	76 (5.8)	761 (6.8)	26 (3.1)
Managerial	3156 (38.8)	477 (36.5)	3996 (35.8)	260 (31.3)
Skilled, non-manual	1000 (12.3)	165 (12.6)	2195 (19.7)	203 (24.5)
Skilled, manual	2056 (25.3)	324 (24.8)	2336 (21.0)	161 (19.4)
Semi-skilled	1047 (12.9)	211 (16.1)	1458 (13.1)	126 (15.2)
Non-skilled	218 (2.7)	55 (4.2)	401 (3.6)	54 (6.5)
Current smoker, No (%)	946 (11.5)	206 (15.3)	1260 (11.1)	125 (14.5)
Prevalent diabetes, No (%)	211 (2.6)	97 (7.2)	223 (2.0)	68 (7.9)
BMI, Jk/m^2, mean (SD)	26.3 (3.2)	27.0 (3.5)	26.0 (4.2)	26.9 (4.4)
T-C, mean (SD), mmol/l	6.0 (1.1)	6.2 (1.1)	6.2 (1.2)	6.7 (1.2)
HDL-C, mean (SD), mmol/l	1.24 (0.33)	1.20 (0.33)	1.6 (0.4)	1.5 (0.4)
Systolic blood pressure, mean (SD), mm Hg	135.8 (16.9)	144.4 (19.1)	132.6 (18.4)	143.4 (19.5)
HbA1c, mean (SD), %	5.3 (0.8)	5.7 (1.2)	5.2 (0.8)	5.8 (1.2)
Use of lipid-lowering drugs, n(%)	55 (0.7)	31 (2.3)	118 (1.0)	31 (3.6)
Use of diabetes drugs, n(%)	138 (1.7)	76 (5.6)	116 (1.0)	52 (6.0)
Use of antihypertensive drugs, n(%)	990 (12.0)	446 (33.1)	1759 (15.4)	367 (42.4)

Table 11: Chamnan 2010[289]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-D'Agostino. CVD events	Patient enrolment: from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: 5% Index test bias Overall: low	Analysis method: Length of follow-up: 11.0 years. Adequate. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	No. of events: >100 events Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	Low

Table 12: Coleman 2007[328]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Coleman 2007. Framingham, SCORE, and	Cohort study, (UKPDS). UK (23 centres).	n=3898 Inclusion criteria: age 25-65; newly diagnosed	Baseline examination between 1997-1991. Baseline	Framingham-Anderson (SCORE and DECODE not extracted)	10-year fatal CVD event rate: 7.4% (6.5-8.3) 10-year fatal CHD event rate:	Median: 10.4 years (range: 6-20).	Framingham, fatal CVD		.
							AUC	0.76	
							Framingham, absolute risk (10-year fatal CVD event rate)		
							Absolute risk	5.0% (underestima	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care. May 2007 vol. 30 no. 5 1292-1293. Funding: not stated.		type 2 diabetes. Exclusion criteria: severe vascular disease, myocardial infarction, or stroke within 1 year and major systemic illness.	characteristics: 59% male, 30% current smokers, mean ± SD age 53 ± 9 years, systolic blood pressure 135 ± 19 mmHg, total cholesterol 5.4 ± 1.1 mmol/l, HDL cholesterol 1.07 ± 0.24 mmol/l, and A1C 7.2 ± 1.8%.		6.6% (5.5-7.1)			te the observed rate by 32%)	
							Framingham, absolute risk (10-year fatal CHD event rate)		
							Absolute risk	4.3% (underestimate the observed rate)	

Table 13: Coleman 2007[328]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham. Fatal CHD events Fatal CVD events	Patient enrolment: referred from general practice. Study Design: prospective	Imputation: No imputation. Lost to follow up: not stated	Analysis method adequate: Length of follow-up: 10.4 years. Adequate	No. of events: >100. Adequate Comments: the paper reports 10-	Population: appropriate to review question. Index test: appropriate to	Unclear

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	cohort. Validation: . Selection bias overall: low	Index test bias overall: unclear	Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: Patient outcome bias overall: low	year event rate Other bias overall: unclear	review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 14: Collins 2012B[337]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Collins 2012B. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and	Cohort study. THIN database. 364 general practices in the UK.	n=2,084,445 Inclusion criteria: age 30-85. Exclusion criteria: patients who had a previous diagnosis of cardiovascular disease,	Patient registered from 27 June 1994 and 30 June 2008. Baseline characteristics: see Table 15.	- QRISK2 - modified Framingham tool	First diagnosis of CVD (myocardial infarction, angina, CHD, stroke, transient ischaemic attacks). n=93,564 (42,224 in	Median 5.75 years (interquartile range 2.48-8.49)	QRISK2 (women)		Method of imputing missing values (smoking status and BMI): multiple imputation using all predictors plus the
							R^2	48.3 (47.9–48.7)	
							D statistic	1.98 (1.96–1.99)	
							ROC statistic	0.835 (0.834–0.837)	
							QRISK2 (men)		
							R^2	41.6 (41.2–42.0)	

external validation of an updated version of QRISK2. BMJ 2012. Funding: this research received no specific grant from any funding agency in the public, commercial, or not for profit sectors		were registered for less than 12 months with the general practice, had invalid dates, had missing Townsend scores (social deprivation), or were prescribed statins at baseline.			women)		D statistic	1.73 (1.71–1.75)	outcome variable. This involves creating multiple copies of the data and imputing the missing values for each dataset with sensible values randomly selected from their predicted distribution. Ten imputed datasets were generated and we combined the results from analyses on each of the imputed values using Rubin's rules to produce estimates and confidence intervals that incorporate
							ROC statistic	0.809 (0.807–0.811)	
							Modified Framingham (women)		
							R^2	34.2 (33.6–34.9)	
							D statistic	1.48 (1.46–1.50)	
							ROC statistic	0.776 (0.773–0.779)	
							Modified Framingham (men)		
							R^2	29.2 (28.7–29.7)	
							D statistic	1.31 (1.30–1.33)	
							ROC statistic	0.750 (0.747–0.752)	

									the uncertainty of imputed values.

Table 15: Collins 2012B[337] baseline characteristics of patients aged 30 to 84 years in The Health Improvement Network database. Values are numbers (percentages) of patients unless stated otherwise

Characteristics	Women (n=1 066 127)	Men (n=1 018 318)
Mean (SD) age (years)	49.6 (14.7)	47.7 (13.4)
Mean (SD) body mass index (mg/kg2)	26.0 (5)	26.5 (4.1)
Body mass index not recorded	220 012 (20.6)	300 787 (29.5)
Mean (SD) systolic blood pressure (mm Hg)	130.5 (21.3)	134.3 (19.0)
Systolic blood pressure not recorded	84 802 (8.0)	183 852 (18.1)
Mean (SD) total cholesterol: HDL cholesterol ratio	3.9 (1.2)	4.5 (1.4)
Total cholesterol: HDL cholesterol ratio not recorded	830 407 (77.9)	791 281 (77.7)
Smoking status:		
Non-smoker	608 942 (57.1)	440 245 (43.2)
Former smoker	154 544 (14.5)	180 952 (17.8)
Current smoker (cigarettes/day):		
Light (<10)	58 254 (5.5)	56 176 (5.5)
Moderate (10-19)	96 970 (9.1)	92 200 (9.1)
Heavy (≥20)	69 517 (6.5)	102 955 (10.1)
Amount not recorded	11 760 (1.1)	29 072 (2.9)
Smoking status not recorded	66 140 (6.2)	116 718 (11.5)
Ethnic group:		
White/not recorded	1 041 209 (97.7)	994 798 (97.7)
Indian	5793 (0.5)	5907 (0.6)

Characteristics	Women (n=1 066 127)	Men (n=1 018 318)
Pakistani	1648 (0.2)	1786 (0.2)
Bangladeshi	520 (0.1)	708 (0.1)
Other Asian	2887 (0.3)	2774 (0.3)
Black Caribbean	2893 (0.3)	2238 (0.2)
Black African	4422 (0.4)	3900 (0.4)
Chinese	1142 (0.1)	848 (0.1)
Other, including mixed race	5613 (0.5)	5359 (0.5)
Clinical condition:		
Treated hypertension	68 061 (6.4)	45 079 (4.4)
Type 2 diabetes	18 295 (1.7)	22 056 (2.2)
Family history of early coronary heart disease	46 974 (4.4)	38 491 (3.8)
Atrial fibrillation	6276 (0.6)	7474 (0.7)
Chronic renal disease	1579 (0.15)	1467 (0.1)
Cardiovascular disease*	42 224	51 340
Person years of observation	6 159 929	5 702 452

**Cardiovascular disease events before death and deaths due to cardiovascular disease*

Table 16: Collins 2012B[337]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
QRISK2. First recorded diagnosis of CVD	Patient enrolment: consecutive. Study Design: retrospective cohort. Validation: adequate	Imputation: adequate method of imputation. Threshold selected: 20%	Analysis method: time to event analysis Length of follow-up: appropriate. Missing outcome	No. of events: ≥100 events Comments: 93,564 CV events recorded; data quality poor (GP database)	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome:	Low

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	Validation. Selection bias overall: low	Index test bias overall: low	data: no missing data. Patient outcome measurement: acceptable. Comments: Data from national primary care database Patient outcome bias overall: low	Other bias overall: high	appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 17: Cooper 2005[350]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Cooper 2005. A comparison of the PROCAM and Framingham point-scoring systems for estimation	Cohort study. Second Northwick Park Heart Study (NPHS-II). From 9 general practices in the UK.	n=2732 men Inclusion criteria: age 50-64; men. Exclusion criteria: not stated.	Baseline characteristics: healthy Caucasian men.	Framingham-Anderson	n=219 CHD events (153 acute CHD events, 45 coronary artery revascularisation procedures, 21 silent MI).	10.8 years (mean)			HDL-C and LDL-C were not measured at baseline and so levels for these variables were set to the average observed in a subset of over 2000
							AUC (95%CI)	0.62 (0.58-0.66)	
							Calibration	Overestimation of the risk (p<0.0001)	
							Ratio observed: predicted	0.47	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
of individual risk of coronary heart disease in the Second Northwick Park Heart Study. Atherosclerosis, 181 (1) 93 - 100. Funding: the British Heart Foundation.									NPHS-II men after 5 years of follow up (LDL-C: 4.0 mmol/l; HDL-C: 0.8 mmol/l).

Table 18: Cooper 2005[350]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. CHD events and with diabetes	Patient enrolment: from general practice. Study Design: prospective	Imputation: LDL-C: 4.0 mmol/l; HDL-C: 0.8 mmol/l. Lost to follow up: not stated	Analysis method: ROC curves Length of follow-up: 10 years.	No. of events: >100 events (n=219) Comments:	Population: appropriate to review question. Index test: appropriate to	High

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	cohort. Validation: . Selection bias overall: low	Index test bias overall: high	Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	Other bias overall: low	review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 19: Elkeles 2008[461]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Elkeles 2008. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients	Cohort study, (PREDICT) UK	n=589 Baseline Examination between 2000-2003. Outpatient diabetes clinics in Central and West London, UK.	Baseline characteristics (%): Coronary artery calcification (AU) CACS 0–10 138 (23.4) CACS 11–100 150 (25.5) CACS 101–400	Framingham-Anderson UKPDS	CVD events n=66 (first CV events, including 10 strokes) CHD events n=56	Median: 4 years (IQR: 30.-4.2).	Framingham, CHD		.
							AUC	0.63 (0.55-0.71)	
							UKPDS, CHD		
							AUC	0.67 (0.60-0.75)	
							UKPDS, CVD		
							AUC	0.63 (0.56-0.71)	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
with type 2 diabetes: the PREDICT study. European Heart Journal (2008) 29, 2244–2251. Funding: Financial support for the PREDICT Study was provided by the Tompkins Foundation and the British Heart Foundation (grant no PG/03/112/16033). The study was also supported by the North West		Inclusion criteria: patients with T2DM (years since diagnosis [mean]: 7 years), free from clinical CVD; age 50-75; Caucasian or Asian. Exclusion criteria: Black African; known coronary artery disease or other cardiac disease; congestive heart failure; uncontrolled hypertension (baseline systolic BP 160 mmHg or diastolic BP 95 mmHg, with or	151 (25.6) CACS 401–1000 89 (15.1) CACS 1001–10000 61 (10.4) Male 373 (63.3) Caucasian 419 (71.1) Asian Indian 120 (20.4) Non-smoker 261 (44.3) Ex-smoker 239 (40.6) Current cigarette smoker 89 (15.1) Other current smoker 34 (5.8) Alcohol (.28 units/week) 35 (5.9) Exercise (regular or aerobic) 466 (79.1) Oral						

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
London Diabetes Local Research Network. I.F.G. is supported by the Heart Disease and Diabetes Research Trust.		without anti-hypertensive treatment); pregnancy; inability to provide informed consent; or other medical conditions likely to limit life expectancy or requiring extensive medical treatment.	hypoglycaemic therapy 475 (80.6) Insulin therapy 147 (25.0) Statin therapy 225 (38.2) Fibrate therapy 49 (8.3) BP-lowering therapy 373 (63.3) Metabolic syndrome (IDF) 440 (74.7) Median (IQR) Age (years) 63.1 (56.8, 68.5) Duration of diabetes (years) 7 (3, 13) BMI (kg/m^2) 28.7 (25.5, 32.2) Waist circumference (cm) 99 (90.5, 108)						

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
			Waist hip ratio (100) 96.6 (90, 102.1) Systolic BP (mmHg) 131 (121, 142) Diastolic BP (mmHg) 78 (72, 84) Heart rate (per min) 74 (66, 81) HbA1c (%) 7.7 (6.9, 9.2) Fasting plasma glucose (mmol/L) 8.9 (7.3, 11.5) Urine albumin creatinine ratio 1.2 (0.7, 3.3) Serum creatinine (mmol/L) 98 (90, 109) Total cholesterol (mmol/L) 4.7 (4.1, 5.4) LDL cholesterol (mmol/L) 2.7						

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
			(2.2–3.3) HDL cholesterol (mmol/L) 1.1 (0.9, 1.3) Triglycerides (mmol/L) 1.5 (1.2, 2.3) Triglycerides HDL cholesterol ratio 1.4 (0.9, 2.2) Total/HDL cholesterol ratio 4.1 (3.4, 5) Fasting plasma insulin (pmol/L) 0.9 (0.4, 2.3) HOMA-IR 0.3 (0.2, 1) Apolipoprotein AI (mg/dL) 141.9 (125.4, 162.4) Apolipoprotein B (mg/dL) 95.9 (81.5, 109.6) ApoAI/ApoB						

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
			ratio 1.5 (1.2, 1.8) Fibrinogen (g/L) 3.3 (2.7, 3.9) C-reactive protein (mg/dL) 0.3 (0.1, 0.5) Homocysteine (mmol/L) 10.3 (8.3, 12.7).						

Table 20: Elkeles 2008[461]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham, UKPDS. CHD events CVD events	Patient enrolment: outpatient diabetes clinic. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: not stated. Index test bias overall: unclear	Analysis method adequate Length of follow-up: 4 years. Too short. Missing outcome data: not stated Patient outcome measurement:	No. of events: <100. Adequate Comments: 66 CVD events Other bias overall: High	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement:	High

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			acceptable. Comments: Patient outcome bias overall: High		acceptable Country: UK Overall applicability: direct	

Table 21: Guzder 2005[602]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Guzder 2005. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed Type 2	Cohort study, community based. UK (people from 24 GP practices whose registered patients live in the Poole Hospital catchment area).	n=428 Inclusion criteria: age 30-75; newly diagnosed type 2 diabetes. Exclusion criteria: stress-related hyperglycaemia.	Baseline examination between 1996-1995. Baseline characteristics: see Table 22.	UKPDS Framingham-Anderson	CVD: n=98 CHD: n=60	Median: 4.2(0.6) years.	Framingham, CVD		.
							Ratio predicted/ observed	0.67	
							AUC	0.673 (0.612-0.734)	
							Framingham, CHD		
							Ratio predicted/ observed	0.68	
							AUC	0.657 (0.581-0.732)	
							UKPDS, CHD		
							Ratio predicted/ observed	0.87	
							AUC	0.670	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
diabetes: results from a United Kingdom study. Diabetic Medicine, 22, 554-562. Funding: Diabetes UK and Takeda UK.								(0.598-0.742)	

Table 22: Guzder 2005[602]: baseline characteristics

Variable	CVD (n=440) median (IQR)
Age (years)	58.6 (±11.1)
Males	241 (56%)
Females	187 (44%)
HbA1c (%)	10.3 (8.0-12.1)
SBP (mmHg)	142 (±21.4)
DBP (mmHg)	81 (±12.1)
T-C (mmol/l)	5.9 (±1.1)
LDL-C (mmol/l)	3.6 (±0.9)

Variable	CVD (n=440) median (IQR)
HDL-C (mmol/l)	1.11 (0.93-1.30)
T-C:HDL	5.4 (±1.6)
Triglycerides (mmol/l)	2.0 (1.48-2.8)
BMI (kg/m^2)	31.5 (±7)
Active smokers	100 (23%)
Antihypertensives at diagnosis	136 (32%)
Lipid-lowering therapy	5 (1%)
Antiplatelet therapy	12 (3%)
LVH on ECG	22 (5.5%)

Data presented as mean (SD) or percentage (number).

Table 23: Guzder 2005[602]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
UKPDS Framingham CHD events CVD events	Patient enrolment: referred from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: excluded from analysis. Index test bias overall: low	Analysis method adequate: Length of follow-up: too short (4.2 years). Missing outcome data: not stated Patient outcome measurement: acceptable. Comments:	No. of events: <100 Comments: Other bias overall: high	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability:	High

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			Patient outcome bias overall: high		direct	

Table 24: Hippisley-Cox 2008[652]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Hippisley-Cox 2008. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008. Funding: No external funding. The authors were funded as part of their clinical or	Cohort study. QRESEARCH database. 531 practices in England and Wales. Derivation (2/3 of practices) and internal validation (1/3 of practices) of QRISK2.	n=2,285,815 Inclusion criteria: age 35-74 at study entry. Exclusion criteria: patients with a prior recorded diagnosis of cardiovascular or cerebrovascular disease, temporary residents, patients with interrupted periods of registration	Patients registered from 1 Jan 1993 and 31 March 2008. Baseline characteristics: see Table 25	- QRISK2 - NICE-Framingham (validation cohort) See Table 26 for adjusted hazard ratios for QRISK2 model.	First recorded diagnosis of CVD: coronary heart disease (angina and myocardial infarction), stroke, or transient ischaemic attacks in the term cardiovascular disease but not peripheral vascular disease. n=96,709 (41,042 in women)	Adequate: time to event	QRISK2 (women)		Method of imputing missing values: assumed that the absence of a recorded diagnosis of diabetes or family history is equivalent to the person not having that factor; where ethnicity was not recorded, the person was included on the white ethnic group.
							R^2	43.47 (42.78–44.16)	
							D statistic	1.795 (1.769–1.820)	
							ROC statistic	0.817 (0.814–0.820)	
							Brier score	0.086 (0.083–0.089)	
							QRISK2 (men)		
							R^2	38.38 (37.75–39.01)	
							D statistic	1.615 (1.594–1.637)	
							ROC statistic	0.792 (0.789–0.794)	
							Brier score	0.136 (0.134–0.139)	
							Modified Framingham (women)		

academic positions and meeting expenses were met by the University of Nottingham	UK	with the practice, those who did not have a valid Townsend deprivation score and those who were taking statins at baseline.					R^2	38.87 (38.12–39.62)	
							D statistic	1.632 (1.606–1.658)	
							ROC statistic	0.800 (0.797–0.803)	
							Brier score	0.093 (0.090–0.096)	
							Modified Framingham (men)		
							R^2	34.78 (34.12–35.45)	
							D statistic	1.495 (1.473–1.517)	
							ROC statistic	0.779 (0.776–0.782)	
							Brier score	0.177 (0.174–0.180)	

Table 25: Hippisley-Cox 2008[652]; baseline characteristics

	Derivation cohort		Validation cohort	
	No (%) of women	**No (%) of men**	**No (%) of women**	**No (%) of men**
No of patients	773 291	762 292	375 763	374 469
Total person years observation	5 645 104	5 280 571	2 594 842	2 470 729
Median age (IQR)	49 (41-60)	48 (40-58)	49 (41-59)	47 (40-57)
Ethnicity:				
White or not recorded	752 241 (97.3)	743 159 (97.5)	363 516 (96.7)	363 097 (97.0)
Indian	3635 (0.47)	3693 (0.48)	2241 (0.60)	2200 (0.59)
Pakistani	2035 (0.26)	2033 (0.27)	1114 (0.30)	1246 (0.33)

	Derivation cohort		Validation cohort	
	No (%) of women	No (%) of men	No (%) of women	No (%) of men
Bangladeshi	1213 (0.26)	1269 (0.17)	611 (0.16)	723 (0.19)
Other Asian	1802 (0.16)	1422 (0.19)	1086 (0.29)	988 (0.26)
Black Caribbean	3928 (0.51)	3109 (0.41)	1870 (0.50)	1495 (0.40)
Black African	3655 (0.47)	3316 (0.44)	2423 (0.64)	2201 (0.59)
Chinese	1128 (0.15)	859 (0.11)	675 (0.18)	478 (0.13)
Other including mixed	3654 (0.47)	3432 (0.45)	2227 (0.59)	2041 (0.55)
Risk factors:				
Ethnicity recorded	209 214 (27.1)	181 110 (23.8)	108 540 (28.9)	94 522 (25.2)
BMI recorded	622 741(80.5)	562 278 (73.8)	304 084 (80.9)	274 403 (73.3)
Smoking recorded	703 574 (91.0)	650 460 (85.3)	344 194 (91.6)	319 800 (85.4)
Cholesterol/HDL ratio recorded	265 402 (34.3)	247 116 (32.4)	210 638 (56.1)	125 037 (33.4)
Systolic blood pressure recorded	711 935 (92.1)	647 782 (85.0)	344 967 (91.8)	313 125 (83.6)
Complete BMI and smoking	615 301 (79.6)	554 070 (72.7)	301 016 (80.1)	270 956 (72.4)
Positive family history of CHD	97 448 (12.6)	73 740 (9.7)	48 610 (12.9)	36 761 (9.8)
Current smoker	176 202 (22.8)	208 913 (27.4)	88 672 (23.6)	104 829 (28.0)
Treated hypertension	55 069 (7.12)	42 607 (5.59)	25 953 (6.91)	20 083 (5.36)
Type 2 diabetes	13 127 (1.70)	17 107 (2.24)	6186 (1.65)	8179 (2.18)
Rheumatoid arthritis	7187 (0.93)	2996 (0.39)	3310 (0.88)	1380 (0.37)
Atrial fibrillation	2692 (0.35)	1880 (0.25)	1242 (0.33)	2155 (0.58)
Chronic kidney disease	1227 (0.16)	1117 (0.15)	621 (0.17)	498 (0.13

IQR=interquartile range; BMI=body mass index; HDL=high density lipoprotein cholesterol; CHD=coronary heart disease.

Table 26: Hippisley-Cox 2008[652]; adjusted hazard ratios (95% CI) for cardiovascular disease for QRISK2 model in derivation cohort

	Women	Men

	Women	Men
White/not recorded	1	1
Indian	1.43 (1.24 to 1.65)	1.45 (1.29 to 1.63)
Pakistani	1.80 (1.5 to 2.17)	1.97 (1.70 to 2.29)
Bangladeshi	1.35 (1.06 to 1.72)	1.67 (1.40 to 2.01)
Other Asian	1.15 (0.86 to 1.54)	1.37 (1.09 to 1.72)
Black Caribbean	1.08 (0.94 to 1.24)	0.62 (0.53 to 0.73)
Black African	0.58 (0.42 to 0.82)	0.63 (0.47 to 0.85)
Chinese	0.69 (0.44 to 1.10)	0.51 (0.32 to 0.83)
Other	1.04 (0.85 to 1.28)	0.91 (0.75 to 1.10)
Age (10% increase)*	1.66 (1.65 to 1.68)	1.59 (1.58 to 1.60)
BMI (5 unit increase)	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.11)
Townsend score (5 unit increase)	1.37 (1.34 to 1.40)	1.18 (1.16 to 1.20)
Systolic blood pressure (mm Hg) (20 unit increase)	1.20 (1.18 to 1.22)	1.19 (1.17 to 1.20)
Cholesterol/HDL ratio	1.17 (1.16 to 1.18)	1.19 (1.18 to 1.20)
Family history coronary heart disease	1.99 (1.92 to 2.05)	2.14 (2.08 to 2.20)
Current smoker	1.80 (1.75 to 1.86)	1.65 (1.60 to 1.70)
Treated hypertension	1.54 (1.45 to 1.63)	1.68 (1.60 to 1.77)
Type 2 diabetes	2.54 (2.33 to 2.77)	2.20 (2.06 to 2.35)
Rheumatoid arthritis	1.50 (1.39 to 1.61)	1.38 (1.25 to 1.52)
Atrial fibrillation	3.06 (2.39 to 3.93)	2.40 (2.07 to 2.79)
Renal disease	1.70 (1.43 to 2.03)	1.75 (1.51 to 2.02)
Age* BMI interaction	0.976 (0.970 to 0.982)	0.985 (0.979 to 0.991)
Age* Townsend interaction (5 unit increase in score)	0.938 (0.930 to 0.946)	0.973 (0.967 to 0.98)
Age* systolic blood pressure interaction (20 unit increase in systolic blood pressure)	0.966 (0.961 to 0.971)	0.964 (0.96 to 0.969)
Age* family history interaction	0.927 (0.914 to 0.94)	0.923 (0.912 to 0.935)
Age* smoking interaction	0.931 (0.920 to 0.943)	0.932 (0.922 to 0.942)

	Women	Men
Age* treated hypertension interaction	0.952 (0.934 to 0.971)	0.916 (0.901 to 0.931)
Age* type 2 diabetes interaction	0.904 (0.877 to 0.931)	0.902 (0.881 to 0.924)
Age* atrial fibrillation interaction	0.858 (0.795 to 0.926)	0.893 (0.852 to 0.935)

BMI=body mass index; HDL=high density lipoprotein cholesterol.
**All age terms expressed as 10% increase in age (for example, 50 to 55 years).*

Table 27: Hippisley-Cox 2008[652]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
QRISK2. First recorded diagnosis of CVD	Patient enrolment: consecutive. Study Design: retrospective cohort. Validation: adequate Validation. Selection bias overall: low	Imputation: adequate method of imputation. Threshold selected: not stated. Comments: Index test bias overall: low	Analysis method: time to event analysis Length of follow-up: appropriate. Missing outcome data: no missing data. Patient outcome measurement: acceptable. Comments: Data from national primary care database Patient outcome bias overall: low	No. of events: ≥100 events Comments: 96,709 CV events recorded; data quality poor (GP database) Other bias overall: high	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK (England and Wales) Overall applicability: direct	Low

Table 28: Hippisley-Cox 2010[650]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures (10-year model)	Effect sizes	Comments
Hippisley-Cox 2010. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010. Funding: No external funding.	Cohort study. QRESEARCH database. 563 practices in England and Wales. Derivation (2/3 of practices) and internal validation (1/3 of practices) of lifetime QRISK2 tool. UK	n=3,601,918 Inclusion criteria: age 30-84. Exclusion criteria: patients who did not have a postcode related Townsend deprivation score, those who had been prescribed statins before the study start date, and those with pre-existing cardiovascular disease.	Patient registered from 1 Jan 1994 and 30 April 2010. Baseline characterisitcs: see Table 29	QRISK2-2010 (lifetime risk calculator) (also compared to the modified Framingham tool in the validation cohort) **See** Table 30 for adjusted hazard ratios for QRISK2-2010 model.	First recorded diagnosis of CVD or death. CVD includes CHD (angina and MI), stroke, or transient ischaemic attacks but not peripheral vascular disease. n=121,623 (including CV events before death and death due to CVD) and n=148,671 deaths from other causes.	Up to 16 years	QRISK2 (women) R^2 ROC statistic QRISK2 (men) R^2 ROC statistic	 47.0 (46.5–47.5) 0.842 (0.840–0.844) 43.4 (42.9–43.9) 0.828 (0.826–0.830)	Multiple imputation to replace missing values for systolic blood pressure, total cholesterol: HDL cholesterol ratio, smoking status, and BMI.

Table 29: Hippisley-Cos 2010[650]: baseline characteristics of the derivation and validation cohorts. Patients are free from cardiovascular disease and not prescribed statins at baseline. Values are numbers (percentages) of patients unless otherwise stated.

	Derivation cohort (n=2 343 759)	Validation cohort (n=1 267 159)
Women	1 189 845 (50.8)	645 012 (50.9)
Mean (SD) age (years)	48.1 (14.3)	48.0 (14.2)
Mean (SD) Townsend score	−0.2 (3.4)	−0.3 (3.5)
Smoking status:		
Non-smoker	1 176 386 (50.2)	631 545 (49.8)
Former smoker	356 697 (15.2)	193 974 (15.3)
Current smoker (amount not recorded)	99 100 (4.2)	59 178 (4.7)
Light smoker (<10 cigarettes/day)	142 369 (6.1)	71 037 (5.6)
Moderate smoker (10-19/day)	175 419 (7.5)	91 679 (7.2)
Heavy smoker (≥20/day)	136 202 (5.8)	74 056 (5.8)
Smoking status not recorded	257 586 (11.0)	145 690 (11.5)
Ethnic group:		
White or not recorded	2 229 834 (95.1)	1 219 987 (96.3)
Indian	22 598 (1.0)	7 577 (0.6)
Pakistani	11 137 (0.5)	3 663 (0.3)
Bangladeshi	6 432 (0.3)	2 632 (0.2)
Other Asian	12 581 (0.5)	5 032 (0.4)
Caribbean	13 454 (0.6)	4 666 (0.4)
Black African	20 801 (0.8)	9 471 (0.8)
Chinese	5 915 (0.3)	3 068 (0.2)
Other	21 007 (0.9)	11 063 (0.8)
Clinical conditions:		

	Derivation cohort (n=2 343 759)	Validation cohort (n=1 267 159)
Treated hypertension*	132 585 (5.7)	67 986 (5.4)
Type 2 diabetes	40 504 (1.7)	20 868 (1.7)
Family history of early coronary heart disease†	247 981 (10.6)	143 593 (11.3)
Atrial fibrillation	12 031 (0.5)	6 589 (0.5)
Chronic renal disease	3 594 (0.2)	1 917 (0.2)
Clinical values:		
Systolic blood pressure recorded	2 027 470 (86.5)	1 081 944 (85.4)
Mean (SD) systolic blood pressure (mm Hg)	131.9 (20.5)	131.7 (20.5)
BMI recorded	1 773 567 (75.7)	949 434 (74.9)
Mean (SD) BMI (kg/m^2)	26.1 (4.5)	26.1 (4.5)
Smoking status and BMI recorded	1 754 250 (74.9)	937 808 (74.0)
Serum total and HDL cholesterol recorded	692 590 (29.6)	354 853 (28.0)
Mean (SD) total cholesterol:HDL cholesterol ratio	4.2 (1.3)	4.2 (1.3)

**A recorded diagnosis of hypertension and treatment that could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, β blockers, thiazides, or calcium channel blockers.*
†Heart disease in a first degree relative aged <60 years.

Table 30: Hippisley-Cox 2010[650]: adjusted hazard ratios* for cardiovascular disease for individual predictor variables in the derivation cohort of 2 343 759 patients

	Adjusted hazard ratio (95% CI)	
Variables	**Women**	**Men**
Body mass index†	1.32 (1.22 to 1.44)	1.54 (1.45 to 1.63)
Systolic blood pressure (per 20 mm Hg increase)	1.13 (1.12 to 1.14)	1.11 (1.10 to 1.12)
Total cholesterol:HDL cholesterol ratio (per unit increase)	1.17 (1.16 to 1.18)	1.18 (1.17 to 1.18)
Townsend score (per 5 unit increase)‡	1.13 (1.11 to 1.14)	1.06 (1.05 to 1.07)

Variables	Adjusted hazard ratio (95% CI)	
	Women	**Men**
Smoking status:		
Non-smoker	1.00	1.00
Former smoker	1.17 (1.14 to 1.21)	1.18 (1.16 to 1.21)
Light smoker (<10 cigarettes/day)	1.39 (1.33 to 1.45)	1.38 (1.34 to 1.43)
Moderate smoker (10-19/day)	1.57 (1.52 to 1.63)	1.55 (1.51 to 1.60)
Heavy smoker (≥20/day)	1.84 (1.77 to 1.91)	1.79 (1.74 to 1.84)
Ethnic group:		
White or not recorded	1.00	1.00
Indian	1.42 (1.28 to 1.58)	1.50 (1.38 to 1.63)
Pakistani	2.04 (1.78 to 2.34)	2.05 (1.84 to 2.28)
Bangladeshi	1.61 (1.30 to 1.98)	2.14 (1.85 to 2.46)
Other Asian	1.14 (0.92 to 1.4 0)	1.32 (1.12 to 1.56)
Caribbean	1.03 (0.91 to 1.16)	0.71 (0.63 to 0.81)
Black African	0.69 (0.54 to 0.89)	0.70 (0.56 to 0.86)
Chinese	0.77 (0.55 to 1.08)	0.79 (0.58 to 1.06)
Other	0.99 (0.85 to 1.16)	0.90 (0.78 to 1.04)
Clinical conditions:		
Family history of early coronary heart disease§	1.67 (1.63 to 1.71)	1.84 (1.80 to 1.88)
Type 2 diabetes	1.67 (1.60 to 1.73)	1.60 (1.55 to 1.66)
Treated hypertension	1.33 (1.30 to 1.36)	1.37 (1.34 to 1.40)
Rheumatoid arthritis	1.43 (1.35 to 1.53)	1.37 (1.26 to 1.50)
Atrial fibrillation	1.89 (1.78 to 2.01)	1.63 (1.54 to 1.72)
Chronic renal disease	1.67 (1.44 to 1.95)	1.59 (1.39 to 1.83)

**Hazard ratios were adjusted for all other variables listed in the table.*
†Fractional polynomial terms for body mass index: for women, (body mass index/10)0.5; for men, ln(body mass index/10).
‡Increasing Townsend scores indicate increasing levels of deprivation.
§Heart disease in a first degree relative aged <60 years.

Table 31: Hippisley-Cox 2010[650]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
QRISK2. First recorded diagnosis of CVD or death	Patient enrolment: consecutive. Study Design: retrospective cohort. Validation: adequate Validation. Selection bias overall: low	Imputation: adequate method of imputation. Threshold selected: not stated. Comments: Index test bias overall: low	Analysis method: time to event analysis Length of follow-up: appropriate. Missing outcome data: no missing data. Patient outcome measurement: acceptable. Comments: Data from national primary care database Patient outcome bias overall: low	No. of events: ≥100 events; data quality: poor (GP database) Other bias overall: high	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK (England and Wales) Overall applicability: direct	Low

Table 32: Kothari 2002[790]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Kothari 2002.	UKPDS is originally	n=4549	Baseline examination	UKPDS	N=188 Strokes, first	10.7 years (median)			.

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke. 2002 Jul;33(7):1776-81. Funding: The major grants for this study were from the United Kingdom Medical Research Council; British Diabetic Association; UK	a landmark RCT. UKPDS cohort used to derive the model. UK	Inclusion criteria: age 25-65 years with newly diagnosed diabetes; fasting plasma glucose >6mmol/litre on 2 further occasions; no recent history of MI, angina or heart failure Exclusion criteria: Patients with a MI within the last year, or with more than 1 vascular episode; people of ethnic group other than white, Afro-Caribbean or Asian-Indian;	between 1977-1991. Baseline characteristics: see Table 33		incidence (n=52 fatal, n=136 non-fatal)				

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Department of Health; National Eye Institute and National Institute of Digestive, Diabetes, and Kidney Disease of the National Institutes of Health; British Heart Foundation; Novo Nordisk; Bayer; Bristol-Myers Squibb; Hoechst; Lilly; Lipha; and Farmalita Carlo Erba. R.J.S. was supported by Wellcome		patients with stroke before diagnosis of diabetes; missing data for blood pressure, electrocardiography or lipids; people with follow up time too short for the model fitting process (<4 years).							

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Trust Fellowship.									

Table 33: Kothari 2002[790]: baseline characteristics

Variable	Men (n=2671)	WOMEN (N=1878)
At diagnosis of diabetes		
Age (years)	51.5 (8.8)	52.6 (8.8)
White Caucasian (%)	81 (2171)	84 (1583)
Afro-Caribbean (%)	7 (198)	8 (153)
Asian-Indian (%)	11 (302)	8 (142)
Current smoker (%)	34 (908)	25 (471)
AF	0.7 (18)	0.5 (10)
BMI	26.5 (5.0)	28.8 (6.0)
Mean of values 1 and 2 years after diagnosis of diabetes		
HbA1c (%)	6.6 (1.4)	6.9 (1.5)
SBP (mmHg)	133 (18)	139 (21)
T-C (mmol/l)	5.2 (1.0)	5.7 (1.1)
HDL-C (mmol/l)	1.06 (0.23)	1.18 (0.26)
T:H	5.2 (1.4)	5.1 (1.5)

Data presented as mean (SD) or percentage (number).

Table 34: Kothari 2002[790]: QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
UKPDS. Stroke	Patient enrolment: referred from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: not stated Index test bias overall: unclear	Analysis method adequate: Length of follow-up: 10.7 years. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	No. of events: >100 Comments: the paper describes derivation of UKPDS (for stroke) and reports the beta coefficients Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	Low

Table 35: Jones 2001 [719]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Jones 2001. Comparativ	Cohort study.	n=691 Inclusion	Baseline examination between 1998-	Framingham-Wilson	n=not clear CHD	10 years	27% threshold (CHD) Sensitivity	 67.0 (53.7-77.3)	.

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
e accuracy of cardiovascular risk prediction methods in primary care patients. Funding: not stated.	12 primary care practices in Birmingham. UK	criteria: age 30-70 years Exclusion criteria: left ventricular hypertrophy.	1999. Baseline characteristics: see Table 36 .				Specificity	97.6 (96.0-98.7)	
							15% threshold (CHD)		
							Sensitivity	82.4 (77.0-86.9)	
							Specificity	93.9 (91.0-96.1)	

Table 36: Jones 2001 [719]; Baseline characteristics

	Male (n=402)	Female (n=289)
Age (years)	53.5 (10.2)	550. (10.0)
SBP (mmHg)	143.8 (21.9)	144.2 (22.0)
T-C (mmol/l)	5.88 (1.11)	6.12 (1.25)
HLD-C (mmol/l)	1.15 (0.37)	1.47 (0.51)
Current cigarette smoking (%)	22.6	18.7
Diabetes mellitus (%)	20.9	18.7

Table 37: Jones 2001[719]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Wilson CHD	Patient enrolment: referred from general practice. Study Design: cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: not stated Index test bias overall: unclear	Analysis method adequate: Length of follow-up: 10 years. Adequate. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: unclear	No. of events: not stated Other bias overall: high	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	High

Table 38: May 2006[934]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes (20% risk threshold)	Comments
May 2006. Cardiovascular disease risk assessment in older women: can	Cohort study. The British Women's Heart and	n=3582 women Inclusion criteria: age 60-79; women. Exclusion criteria: CHD	Women recruited between 1999 and 2001, from 23 British towns. Baseline	Framingham-Anderson	n= 198 CHD events. n=240 CVD events	4.7 years (median)	CHD event		
							Ratio predicted/ observed	1.03	
							AUC	0.59 (0.56-0.63)	
							Sensitivity (30%	10%	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes (20% risk threshold)	Comments
we improve on Framingham? British Women's Heart and Health prospective cohort study. Heart. 2006 October; 92(10): 1396–1401. Funding: UK Department of health, British Heart Foundation, the Medical Research Council.	Health Study.	and CVD at baseline.	characteristics: .				threshold)		
							Specificity (30% threshold)	95%	
							CVD event		
							Ratio predicted/ observed	1.54	
							AUC	0.62 (0.58-0.65)	
							Sensitivity (30% threshold)	38%	
							Specificity (30% threshold)	79%	

Table 39: May 2006[934]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. CHD events CVD events	Patient enrolment: from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: some variable imputed (<11%). Method of imputation not stated. Lost to follow up: not stated Index test bias overall: high	Analysis method: Length of follow-up: 4.7 years. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	No. of events: >100 events Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	High

Table 40: Ramachandran 2000[1125]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Ramachandran 2000. Using the Framingham model to predict heart	Cohort study. A cross section of the population of Whickham, north east	n=1700 Inclusion criteria: age 30-75 years. Exclusion criteria:	.	Framingham-Anderson tool	Heart disease n= 529 (272 in women)	20 years	Calibration results: The agreement is good at a predicted event rate above 30% (1.5% per year), with no significant difference between the observed and expected event rates (P=0.85). However, at lower event rates the		Baseline values for HDL-C not available. Values of 1.15 mmol/l were used for men and 1.4

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
disease in the United Kingdom: retrospective study. BMJ2000;320: 676. Funding: Department of Health and Newcastle District Research Committee	England, was enrolled in a study of ischaemic heart disease between 1972 and 1974. Validation of the Framingham-Anderson tool.	patients with heart disease at baseline; those who had previously been smokers were excluded because the length of time since quitting was unknown.					predictive model significantly underestimates the number of observed events (P<0.01). The wide confidence intervals indicate that there is significant overlap between risk scores in those participants who developed heart disease and those who did not.		mmol/l for women.

Table 41: Ramachandran 2000[1125]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. Heart disease	Patient enrolment: not stated. Study Design: retrospective cohort. Validation: adequate Validation.	Imputation: Baseline values for HDL-C not available. Values of 1.15 mmol/l were used for men and 1.4 mmol/l for women	Analysis method: Not states=d. Length of follow-up: appropriate. Missing outcome data: no missing data.	No. of events: ≥100 events Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow	Very high

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	Selection bias overall: high	Index test bias overall: high	Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low		up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 42: Ramsay 2011[1132]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes (20% risk threshold)	Comments
Ramsay 2011. Prediction of coronary heart disease risk by Framingham and SCORE risk assessments varies by socioeconomic position: results from	Cohort study. The British Regional Heart Study (BRHS).	n=6467 men Inclusion criteria: age 40-59; men; free from CVD. Exclusion criteria: men whose longest-held occupation was in the armed forces and those who did not report their occupation.	Men aged 40-59 years at the baseline (period 1978-80), from 1 general practice in each of 24 towns representing all major British regions. Baseline characteristics: .	Framingham-Anderson	n=647 CHD events.	10 years	Social class I (n=535)		
							Predicted/ observed ratio	2.39 (1.85-2.93)	
							Sensitivity (%)	53 (34-72)	
							Specificity (%)	85 (82-88)	
							Social class II (n=1518)		
							Predicted/ observed ratio	1.87 (1.36-2.37)	
							Sensitivity (%)	56 (47-65)	
							Specificity (%)	79 (77-81)	
							Social class III NM (n=632)		
							Predicted/ observed	1.53 (1.05-	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes (20% risk threshold)	Comments
a study in British men. EUR J CARDIOV PREV R, 18 (2) 186 - 193. Funding: UK MRC Special Training Fellowship in Health Services/Health of the Public Research.							ratio	2.01)	
							Sensitivity (%)	57 (45-69)	
							Specificity (%)	76 (72-79)	
							Social class III M (n=2832)		
							Predicted/ observed ratio	1.55 (1.07-2.03)	
							Sensitivity (%)	54 (49-60)	
							Specificity (%)	73 (71-75)	
							Social class IV (n=679)		
							Predicted/ observed ratio	1.42 (0.93-1.90)	
							Sensitivity (%)	47 (36-59)	
							Specificity (%)	74 (70-77)	
							Social class V (n=271)		
							Predicted/ observed ratio	1.18 (0.70-1.66)	
							Sensitivity (%)	37 (22-54)	
							Specificity (%)	74 (68-79)	
							Non-Manual (n=2685)		
							Predicted/ observed ratio	1.84 (1.33-2.34)	
							Sensitivity (%)	56 (49-63)	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes (20% risk threshold)	Comments
							Specificity (%)	79 (78-81)	
							Manual (n=3782)		
							Predicted/ observed ratio	1.49 (1.01-1.97)	
							Sensitivity (%)	52 (47-56)	
							Specificity (%)	73 (71-75)	

Table 43: Ramsay 2011[1132]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. CHD events	Patient enrolment: from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: not stated. Lost to follow up: not stated Index test bias overall: low	Analysis method: Length of follow-up: 10 years. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	No. of events: >100 events (n=647) Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	Low

Table 44: Simmonds 2012[1260]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Simmonds 2012. Risk estimation versus screening performance: a comparison of six risk algorithms for cardiovascular disease. J Med Screen 2012;19:201–205. Funding: not stated.	Cohort study. Hypothetical sample population	n=500,000 (simulated population) Age: 40-74 years.	Data on the age and sex distribution of the population was obtained from Office of National Statistics data. The distributions, given age and sex, of total and HDL cholesterol, systolic blood pressure, body mass index, C-reactive protein (all assumed Gaussian distributed), smoking and diabetes, were obtained from the 2003 Health Survey for England. Distributions	• Framingham-Anderson. • QRISK2. (Not extracted: • ASSIGN • Framingham D'Agostino • Reynolds • SCORE)	Not stated. Individuals who had a first CVD event in each year of the simulated 10-year follow-up period were identified using Monte Carlo simulation, with the probability of having a CVD event being equal to the estimate of 1-year CVD risk obtained from the Framingham 1991 algorithm. Same process of simulating CVD events for the other 5 risk algorithms.	10 years	Framingham-Anderson Sensitivity (15% threshold) Specificity (15% threshold) QRISK2 Sensitivity (16 years cut off) Specificity (16 years cut off)	79 80 73 80	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
			of other risk factors were based on data presented in the publications of the relevant risk algorithms.						

Table 45: Simmonds 2012; QUADAS II[1260]

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
• Framingham-Andreson. • QRISK2 CVD events.	Patient enrolment: N/A. Study Design: cohort; simulated population. Validation: not adequate Validation. Selection bias overall: High	Imputation:100% imputation. Threshold selected: 15%, 16%. Comments: Index test bias overall: unclear	Analysis method: Length of follow-up: appropriate. Missing outcome data: N/A. Patient outcome measurement:. Comments: Simulation of CVD events based on the Framingham equation for evaluation of Framingham and	No. of events: Not stated; data quality: poor Other bias overall: high	Population:. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: not clear. Country: UK (England and Wales) Overall applicability: direct	Very high

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			based on QRISK2 equation for evaluation of QRISK2. Patient outcome bias overall: very high			

Table 46: Simmons 2008[1262]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Simmons 2008. Evaluation of the Framingham Risk Score in the European Prospective Investigation of Cancer–Norfolk Cohort. Arch Intern Med. 2008;168(1	Cohort study. European Prospective Investigation of Cancer [EPIC]–Norfolk.	n=10295 (n=4513 men and n=5782 women). Inclusion criteria: age 40-79; women. Exclusion criteria: individuals with self-reported CHD at baseline; those with missing values for 1	Patients recruited from general practices in the Norfolk region, England, between March 1993 and February 1998. Baseline characteristics: see Table 47.	Framingham-Wilson	n= 680 CHD events. (n=430 men and n=250 women).	8.5 years (median)	Framingham-Wilson		3 novel risk scores calculated by fitting Cox proportional hazards regression models to the EPIC-Norfolk data, each with the log hazard of CHD as the outcome, separately in men and women, and with
							AUC (men)	0.71 (0.69-0.73)	
							AUC (women)	0.71 (0.38-0.74)	
							Model A		
							AUC (men)	0.72 (0.70-0.74)	
							AUC (women)	0.80 (0.77-0.82)	
							Model B		
							AUC (men)	0.73 (0.70-0.75)	
							AUC (women)	0.80 (0.78-0.83)	
							Model C		

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
1):1209-1216. Funding: the Medical Research Council, Cancer Research UK, the British Heart Foundation, the European Union (Europe Against Cancer Programme), the Stroke Association, Wellcome Trust, Research Into Ageing, and the Academy of Medical Sciences.		or more of the variables used to calculate the Framingham risk score; those with HbA1c values not available.					AUC (men)	0.73 (0.70-0.75)	covariates included as follows: model A: age, T-C, HDL-C, SBP, smoking status, and diabetes mellitus; model B: age, T-C, HDL-C, SBP, smoking status, and HbA1c; and model C: age, T-C, HDL-C, SBP, smoking status, diabetes mellitus, and HbA1c.
							AUC (women)	0.80 (0.78-0.83)	

Table 47: Simmons 2008[1262]; baseline characteristics

Characteristic	Men (n=4513)	Women (n=5782)
Age, mean (SD), years	58.3 (9.7)	57.6 (9.6)
Social Class, No (%)		
Professional	369 (8.3)	455 (8.0)
Managerial	1696 (38.2)	2056 (36.2)
Skilled, non-manual	575 (12.9)	1068 (18.8)
Skilled, manual	1105 (24.9)	1195 (21.0)
Semi-skilled	563 (12.7)	727 (12.8)
Non-skilled	133 (3.0)	178 (3.1)
T-C, mean (SD), mg/dl	232 (42)	239 (46)
HDL-C, mean (SD), mg/dl	50 (12)	62 (19)
Systolic blood pressure, mean (SD), mm Hg	136.8 (17.0)	132.7 (18.7)
Prevalent diabetes mellitus, No (%)	154 (3.4)	134 (2.3)
Current smoker, No (%)	550 (12.2)	680 (11.8)
HbA1c, mean (SD), %	5.3 (0.9)	5.3 (0.8)

Table 48: Simmons 2008[1262]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Wilson. CHD events	Patient enrolment: from general practice. Study Design: prospective	Imputation: No imputation. Lost to follow up: not stated	Analysis method: Length of follow-up: 8.5 years.	No. of events: >100 events Comments:	Population: appropriate to review question. Index test: appropriate to review question.	Low

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	cohort. Validation: . Selection bias overall: low	Index test bias Overall: low	Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	Other bias overall: low	Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 49: Simmons 2009[1261]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Simmons 2009. Performance of the UK Prospective Diabetes Study Risk Engine and the Framingham Risk Equations in Estimating	Cohort study. European Prospective Investigation of Cancer [EPIC]–Norfolk.	n=10,137 (n=4424 men and n=5713 women). Inclusion criteria: age 40-79; women. Exclusion criteria: individuals with self-reported CVD at baseline;	Patients recruited from general practices in the Norfolk region, England, between March 1993 and February 1998. Age: 40-79 years.	- Framingham-D'Agostino - UKPDS	n=961 CVD events (n=69 subgroup 1; n=160 subgroup 2; n=732 subgroup 3).	10.1 years (median)	AUC UKPDS Subgroup 1	0.72 (0.65-0.78)	
							AUC UKPDS Subgroup 2	0.68 (0.63-0.72)	
							AUC UKPDS Subgroup 3	0.77 (0.76-0.79)	
							AUC Framingham Subgroup 1	0.73 (0.66-0.78)	
							AUC Framingham Subgroup 2	0.66 (0.62-0.71)	
							AUC	0.77	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Cardiovascular Disease in the EPIC–Norfolk Cohort. Diabetes Care, Vol 32, N.4, 2009. Funding: the Medical Research Council, Cancer Research UK, the British Heart Foundation, the European Union (Europe Against Cancer Programme), the Stroke Association, and Research		those with missing values for 1 or more of the variables used to calculate the Framingham risk score and UKPDS Risk Engine.	**Three subgroups**: 1) Individuals with known diabetes (n=272) 2) Individuals with non-diabetics hyperglycemia, defined as A1C≥6.0% (n=906) 3) Individuals with A1C<6.0% (normoglycemia) (n=8959)				Framingham Subgroup 3	(0.76-0.79)	
							Sensitivity (20%) UKPDS Subgroup 1	0.94	
							Sensitivity (20%) UKPDS Subgroup 2	0.94	
							Sensitivity (20%) UKPDS Subgroup 3	0.97	
							Specificity (20%) UKPDS Subgroup 1	0.31	
							Specificity (20%) UKPDS Subgroup 2	0.22	
							Specificity (20%) UKPDS Subgroup 3	0.15	
							Sensitivity (20%) Framingham Subgroup 1	0.86	
							Sensitivity (20%) Framingham Subgroup 2	0.90	
							Sensitivity (20%) Framingham Subgroup 3	0.96	
							Specificity (20%) Framingham Subgroup 1	0.30	
							Specificity (20%) Framingham Subgroup 2	0.26	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Into Ageing.							Specificity (20%) Framingham Subgroup 3	0.20	

Table 50: Simmons 2009[1261]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-D'Agostino. CVD events	Patient enrolment: from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: not stated Index test bias Overall: low	Analysis method: Length of follow-up: 10.1 years. Adequate. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	No. of events: >100 events Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	Low

Table 51: Stephens 2004[1296]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Stephens 2004. Cardiovascular risk and diabetes. Are the methods of risk prediction satisfactory ? European journal of cardiovascular prevention and rehabilitation 2004, 11:521-528. Funding: British Heart Foundation and	Cohort study. UK	n=798 Inclusion criteria: age 35-74; diabetes diagnosed as defined by the WHO Exclusion criteria: pre-existing CVD; renal failure; family history of dyslipidaemia	Diabetes clinic at University College London Hospital NHS Trust (UCLH). Baseline examination between 1990-1991. Baseline characteristics: see Table 52.	UKPDS (JBSRC, CRM, PROCAM not extracted)	CVD: n=358 CHD: n=269	10 years. n=239/1176 loss to follow up. n=65 died	CVD		.
							AUC	0.74 (0.70-0.78)	
							CHD		
							AUC	0.76 (0.72-0.80)	
							Poor calibration (P<0.001): overprediction		
							CVD		
							Conversion factor	1.2	
							CHD		
							Conversion factor	1.6	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Diabetes UK.									

Table 52: Stephens 2004[1296]; baseline characteristics

Variable	CVD (n=440) median (IQR)	No CVD (N=358) median (IQR)	P value
Age (years)	63 (56-69)	54 (44-61)	<0.001
HbA1c (%)	10.2 (9.0-11.8)	10.3 (8.8-11.8)	0.56
Glucose (mmol/l)	9.9 (6.9-13.9)	8.9 (6.1-13.0)	0.03
T-C (mmol/l)	6.1 (5.4-6.9)	5.5 (4.8-6.4)	<0.001
LDL-C (mmol/l)	4.9 (4.2-5.7)	4.2 (3.5-5.0)	<0.001
HDL-C (mmol/l)	1.0 (0.9-1.4)	1.2 (1.0-1.6)	<0.001
T-C:HDL	5.7 (4.5-6.8)	4.3 (3.3-5.5)	<0.001
Triglycerides (mmol/l)	2.2 (1.4-3.7)	1.5 (0.9-2.5)	<0.001
BMI (kg/m^2)	27.0 (24.6-30.0)	25.6 (23.2-28.9)	<0.001
SBP (mmHg)	140 (127-155)	135 (12-149)	0.001
DBP (mmHg)	78 (70-86)	78 (71-85)	0.76
Duration of diabetes (years)	13 (8-24)	12 (7-21)	0.05
Male sex (%)	68.4	58.5	0.01
Smoker (%)	21.6	17	0.01
Type 1/Type 2 DM (%)	37.3/62.3	32.8/47.2	0.03
Caucasian (%)	47	46	0.71

Data presented as mean (SD) or percentage (number).

Table 53: Stephens 2004[1296]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
UKPDS. CHD events CVD events	Patient enrolment: referred from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: No imputation. Lost to follow up: excluded from analysis. Index test bias overall: low	Analysis method adequate: Length of follow-up: 10 years. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: Patient outcome bias overall: low	No. of events: >100 Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: Direct	Low

Table 54: Stevens 2001[1297]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Stevens 2001. The UKPDS	UKPDS is originally a landmark	n=4540 Inclusion criteria: age	Baseline examination between 1977-1991.	UKPDS	CHD (fatal or non-fatal MI or sudden death) first incidence.	10.7 years (median)			Derivation of the UKPDS model.

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin-Sci-(Lond). 2001 Dec; 101(6): 671-9. Funding: grant from the Wellcome Trust.	RCT. UKPDS cohort used to derive the model. UK	25-65 years with newly diagnosed diabetes; fasting plasma glucose >6mmol/l on 2 further occasions; no recent history of MI, angina or heart failure Exclusion criteria: people of ethnic group other than white, Afro-Caribbean or Asian-Indian; missing data for HbA1c, SBP or lipids; people with follow up time too short for the model fitting process (<4	Baseline characteristics: see Table 55.						

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
		years).							

Table 55: Stevens 2001[1297]; baseline characteristics

Variable	Men (n=2643)	WOMEN (N=1897)
At diagnosis of diabetes		
Age (years)	51.5 (8.8)	52.7 (8.7)
White Caucasian (%)	81 (2151)	85 (1603)
Afro-Caribbean (%)	7.6 (201)	8.1 (153)
Asian-Indian (%)	11 (291)	7.4 (141)
Smoker (%)	34 (898)	25 (474)
BMI	27.7 (4.6)	30.4 (6.3)
Mean of values 1 and 2 years after diagnosis of diabetes		
HbA1c (%)	6.6 (1.4)	6.9 (1.5)
SBP (mmHg)	133 (18)	139 (21)
T-C (mmol/l)	5.2 (1.0)	5.7 (1.1)
HDL-C (mmol/l)	1.06 (0.23)	1.18 (0.27)

Data presented as mean (SD) or percentage (number).

Table 56: Stevens 2001[1297]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
UKPDS.	Patient enrolment: referred from	Imputation: No imputation.	Analysis method adequate:	No. of events: not stated	Population: appropriate to	Low

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
CHD events CVD events	general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Lost to follow up: not stated Index test bias overall: unclear	Length of follow-up: 10.7 years. Missing outcome data: not stated Patient outcome measurement: acceptable. Comments: . Patient outcome bias overall: low	Comments: the paper describes derivation of UKPDS (for CVD and CHD) and reports the beta coefficients Other bias overall: unclear	review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: acceptable Country: UK Overall applicability: direct	

Table 57: Wald 2011[1397]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Wald 2011. Screening for Future Cardiovascular Disease Using Age Alone Compared	Cohort study. Hypothetical sample population	n=500,000 (simulated population) Age: 0-89 years.	The sample population was generated having the same age and sex distributions as England and Wales (2007)	• Framingham-Anderson. • Age alone.	465 CVD events per 10,000 patients. Simulation of CVD events: CVD events were simulated by performing random	10 years	Framingham-Anderson		
							Sensitivity (20% threshold)	66	
							Specificity (20% threshold)	91	
							Sensitivity (8% threshold)	86	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
with Multiple Risk Factors and Age. PLoS One. 2011; 6(5): e18742. Funding: The authors have no support or funding to report.			using Monte Carlo simulation.		Bernoulli trials for each individual in each year where the probability of success was equal to the 1-year Framingham risk of CHD death, myocardial infarction or stroke for that individual in that year. If the random trial was a success the individual was assumed to have had the relevant CVD event in that year		Specificity (8% threshold)	79	
							Sensitivity (5% threshold)	91	
							Specificity (5% threshold)	73	
							Age alone		
							Sensitivity (66 years cut off)	66	
							Specificity (66 years cut off)	88	
							Sensitivity (55 years cut off)	86	
							Specificity (55 years cut off)	76	
							Sensitivity (50 years cut off)	91	
							Specificity (50 years cut off)	69	

Table 58: Wald 2011[1397]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
• Framingham-Andreson. • Age alone CVD events.	Patient enrolment: N/A. Study Design: cohort; simulated population. Validation: not adequate Validation. Selection bias overall: High	Imputation: 100% imputation. Threshold selected: 20%, 55 years and 50 years. Comments: Index test bias overall: unclear	Analysis method: Length of follow-up: appropriate. Missing outcome data: N/A. Patient outcome measurement:. Comments: Simulation of CVD events based on the Framingham equation Patient outcome bias overall: very high	No. of events: Not stated; data quality: poor Other bias overall: high	Population:. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard measurement: not clear. Country: UK (England and Wales) Overall applicability: direct	Very high

Table 59: Wannamethee 2005[1403]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures (10-year model)	Effect sizes	Comments
Wannamethee 2005. Metabolic	Cohort study. The British	n=5128 men Inclusion criteria: age 40-59; men.	Initial screening Jan 1978-July 1980.	Framingham-Anderson	n=769 major CHD events (fatal CHD and non-fatal MI),	21.3 years (mean)	10 year prediction of CHD events		.
							AUC (95%CI)	0.73 (0.71-0.75)	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures (10-year model)	Effect sizes	Comments
syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. ARCH INTERN MED, 165 (22) 2644 - 2650. Funding: Department of health (England).	Regional Heart Study; from general practices in 24 towns in England, Wales and Scotland. UK	Exclusion criteria: diagnosis of CHD or stroke, known diabetes at screening, and/or asymptomatic hyperglycaemia.	Baseline characteristics: see.Table 60.		n=291 major stroke events (fatal and non-fatal); n=299 type 2 diabetes.		Sensitivity	56.5%	
							Specificity	75.0%	

Table 60: Wannamethee 2005[1403]; baseline characteristics of 5128 men with no history of chd, stroke, or type 2 diabetes mellitus

Characteristic	Value [mean (SD), or median (interquartile range)]
Age, y	50.3 (5.7)

Characteristic	Value [mean (SD), or median (interquartile range)]
Current cigarette smoker, %	42.1
Inactive, %	37.8
Manual social class, %	58.6
Non-drinker, %	5.6
Heavy drinker, %	11.3
BMI	25.4
SBP, mmHg	145.7 (20.7)
DBP, mmHg	83.0 (13.2)
Triglyceride, mmol/l	1.72 (1.17-2.50)
HDL-C, mmol/l	1.15 (0.27)
T-C, mmol/l	6.25 (1.03)
Glucose, mmol/l	5.4 (5.0-5.9)
Metabolic syndrome, %	26.0

Table 61: Wannamethee 2005[1403]; QUADAS II

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
Framingham-Anderson. CHD events, stroke	Patient enrolment: from general practice. Study Design: prospective cohort. Validation: . Selection bias overall: low	Imputation: no imputation. Lost to follow up: <1% Index test bias overall: low	Analysis method: ROC curves Length of follow-up: 20 years. Missing outcome data:<1%. Patient outcome	No. of events: >100 events (n=1060) Comments: Other bias overall: low	Population: appropriate to review question. Index test: appropriate to review question. Patient outcome: appropriate follow up time. Ref standard	Low

Tool, outcome	Selection bias	Index test bias	Patient outcome bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			measurement: acceptable. Comments: . Patient outcome bias overall: low		measurement: acceptable Country: UK Overall applicability: direct	

Table 62: Wilson 1998[1436]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Wilson 1998. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. 1998; 97: 1837-1847. Funding:	Cohort study. Original Framingham and Framingham Offspring Cohorts. Derivation of the Framingham-Wilson tool. USA	n=5345 Inclusion criteria: age 30-74 years at the time of the baseline examination; Exclusion criteria:	Baseline examination between 1971-1974. Baseline characteristics: .	Framingham-Wilson. Risk factors included: • Age • Gender • HDL-C • T-C • SBP • Smoking • Diabetes • ECG-LVH	CHD incidence. n=610 (227 in women)	12 years	AUC associated with T-C categories		Age-adjusted linear regression or logistic regression to test for trends across blood pressure, T-C, LDL-C, and HDL-C categories. Separate score sheet for each sex using T-C and LDL-C categories.
							Men		
							AUC continuous variables	0.74	
							AUC categorical variables	0.73	
							AUC risk factor sum	0.69	
							Women		
							AUC continuous variables	0.77	
							AUC categorical	0.76	

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
							variables		
							AUC risk factor sum	0.72	
							AUC associated with LDL-C categories		
							Men		
							AUC continuous variables	0.74	
							AUC categorical variables	0.73	
							AUC risk factor sum	0.68	
							Women		
							AUC continuous variables	0.77	
							AUC categorical variables	0.77	
							AUC risk factor sum	0.71	

Table 63: Wilson 1998[1436]; β-Coefficients underlying CHD prediction sheets using TC categories

Variable	Men	Women

Variable	Men	Women
Age, y	0.04826	0.33766
Age squared, y		−0.00268
TC, mg/dL		
<160	−0.65945	−0.26138
160–199	Referent	Referent
200–239	0.17692	0.20771
240–279	0.50539	0.24385
≥280	0.65713	0.53513
HDL-C, mg/dL		
<35	0.49744	0.84312
35–44	0.24310	0.37796
45–49	Referent	0.19785
50–59	−0.05107	Referent
≥60	−0.48660	−0.42951
Blood pressure		
Optimal	−0.00226	−0.53363
Normal	Referent	Referent
High normal	0.28320	−0.06773
Stage I hypertension	0.52168	0.26288
Stage II–IV hypertension	0.61859	0.46573
Diabetes	0.42839	0.59626
Smoker	0.52337	0.29246
Baseline survival function at 10 years, S(t)	0.90015	0.96246

Table 64: Wilson 1998[1436]; β-Coefficients underlying CHD prediction sheets using LDL-C categories

Variable	Men	Women
Age, y	0.04808	0.33994
Age squared, y		−0.0027
LDL-C, mg/dL		
<100	−0.69281	−0.42616
100–129	Referent	Referent
130–159	0.00389	0.01366
160–189	0.26755	0.26948
≥190	0.56705	0.33251
HDL-C, mg/dL		
<35	0.48598	0.88121
35–44	0.21643	0.36312
45–49	Referent	0.19247
50–59	−0.04710	Referent
≥60	−0.34190	−0.35404
Blood pressure		
Optimal	−0.02642	−0.51204
Normal	Referent	Referent
High normal	0.30104	−0.03484
Stage I hypertension	0.55714	0.28533
Stage II–IV hypertension	0.65107	0.50403
Diabetes	0.42146	0.61313
Smoker	0.54377	0.29737
Baseline survival function at 10 years, S(t)	0.90017	0.9628

Table 65: Wilson 1998[1436]; β-Coefficients underlying CHD prediction sheets using T-C categories

Variable	Men	Women
Age, y	0.04826	0.33766
Age squared, y		−0.00268
TC, mg/dL		
<160	−0.65945	−0.26138
160–199	Referent	Referent
200–239	0.17692	0.20771
240–279	0.50539	0.24385
≥280	0.65713	0.53513
HDL-C, mg/dL		
<35	0.49744	0.84312
35–44	0.24310	0.37796
45–49	Referent	0.19785
50–59	−0.05107	Referent
≥60	−0.48660	−0.42951
Blood pressure		
Optimal	−0.00226	−0.53363
Normal	Referent	Referent
High normal	0.28320	−0.06773
Stage I hypertension	0.52168	0.26288
Stage II–IV hypertension	0.61859	0.46573
Diabetes	0.42839	0.59626
Smoker	0.52337	0.29246
Baseline survival function at 10 years, S(t)	0.90015	0.96246

Table 66: Wilson 1998[1436]; β-Coefficients underlying CHD prediction sheets using LDL-C categories

Variable	Men	Women
Age, y	0.04808	0.33994
Age squared, y		−0.0027
LDL-C, mg/dL		
<100	−0.69281	−0.42616
100–129	Referent	Referent
130–159	0.00389	0.01366
160–189	0.26755	0.26948
≥190	0.56705	0.33251
HDL-C, mg/dL		
<35	0.48598	0.88121
35–44	0.21643	0.36312
45–49	Referent	0.19247
50–59	−0.04710	Referent
≥60	−0.34190	−0.35404
Blood pressure		
Optimal	−0.02642	−0.51204
Normal	Referent	Referent
High normal	0.30104	−0.03484
Stage I hypertension	0.55714	0.28533
Stage II–IV hypertension	0.65107	0.50403
Diabetes	0.42146	0.61313
Smoker	0.54377	0.29737
Baseline survival function at 10 years, S(t)	0.90017	0.9628

G.2 Dietary interventions

Study	Anon 1965[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=252)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 3.06 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Changes on ECG for diagnosis of MI
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged < 65 years following acute MI.
Exclusion criteria	Long term anticoagulant therapy, syphilis, diabetes, myxoedema, severe hypertension, cardiac enlargement.
Recruitment/selection of patients	Recruited on leaving hospital after MI.
Age, gender and ethnicity	Age - Other: Less than 65 years. Gender (M:F): 100/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Usual diet. Usual diet. Duration mean 3.05 years. Concurrent medication/care: Anticoagulant therapy. Overweight subjects given weight reduction advice (n=123) Intervention 2: Diet intervention - Low fat diet. Daily allowance of 40 g fat including; 14 g butter, 84 g meat, 1 egg, 56 g cottage cheese, skimmed milk. Duration mean 3.05 years. Concurrent medication/care: Anticoagulant therapy. Patient and wife saw doctor and dietician 2 weeks after hospital discharge, then every 2 weeks for 3 months, every 3 months for 2 years and 6-monthly thereafter; dietician checked diaries at every visit and discussed problems

Funding	Academic or government funding (Medical Research Council)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW FAT DIET versus USUAL DIET Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: Mortality at 3 years; Group 1: 20/123, Group 2: 24/129; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Non-fatal reinfarctions at 3 years; Group 1: 27/123, Group 2: 27/129; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study	**Anon 1968[2]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=393)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG evidence of MI
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men after first MI aged < 60 years.
Exclusion criteria	Gross obesity, diabetes, syphilis, hypertension (diastolic BP > 110mm Hg or potent hypotensive drugs required), cardiac lesions prejudicing prognosis, previous significant modification of dietary fat intake, unsuitable for prolonged anticoagulation therapy, inability to understand / comply with dietary regime, previous anticoagulant therapy.
Recruitment/selection of patients	Recruited at discharged from hospital.
Age, gender and ethnicity	Age - Other: < 60 years. Gender (M:F): 393/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=199) Intervention 1: Diet intervention - High polyunsaturated fat diet. As far as possible, saturated fats removed from the diet and participants were instructed to take 85 g soya bean oil daily; up to 35 g of other fat / day allowed, 14 g taken as moderately unsaturated margarine (other foods allowed; lean meat (up to 85 g), any fish, skimmed milk, clear soups, foods forbidden; butter, other margarines, whole milk, cheese, egg yolk, biscuits and cakes). Duration 6 years. Concurrent medication/care: Anticoagulant therapy (n=194) Intervention 2: Usual diet. Usual diet. Duration 6 years. Concurrent medication/care: Anticoagulant therapy
Funding	Academic or government funding (Medical Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: Death at 6 years; Group 1: 28/199, Group 2: 38/194; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD: Non-fatal definite reinfarctions at 6 years; Group 1: 20/199, Group 2: 26/194; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 10 years
- Actual outcome for Adults with established CVD: Cardiovascular disease death at 6 years; Group 1: 27/199, Group 2: 25/194; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years-

Study (subsidiary papers)	**Burr 1989[253] (Burr 1989[254])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2033)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 2 years.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men < 70 years following first MI.
Exclusion criteria	Diabetes and other serious illness.
Recruitment/selection of patients	Recruited from 21 hospitals.
Age, gender and ethnicity	Age - Mean (SD): 56.5 (8.0) years. Gender (M:F): 2033/0. Ethnicity: Not reported.
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=1018) Intervention 1: Diet intervention - Low fat diet. Advice to reduce saturated fat. Duration 2 years. Concurrent medication/care: Anticoagulant, aspirin / antiplatelet, antihypertensive, beta-blocker; dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months (n=257) Intervention 2: Diet intervention - Increased omega-3 fatty acid fish diet. Advice to increase fatty fish consumption. Duration 2 years. Concurrent medication/care: Anticoagulant, aspirin / antiplatelet, antihypertensive, beta-blocker, dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months (n=1017) Intervention 3: Diet intervention - Increased fibre diet. Advice to increase cereal consumption. Duration 2

	years. Concurrent medication/care: Anticoagulant, aspirin / antiplatelet, antihypertensive, beta-blocker; dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months (n=1015) Intervention 4: Usual diet. Sensible eating. Duration 2 years. Concurrent medication/care: Anticoagulant, aspirin / antiplatelet, antihypertensive, beta-blocker (n=252) Intervention 5: Usual diet. Sensible eating. Duration 2 years. Concurrent medication/care: Anticoagulant, aspirin / antiplatelet, antihypertensive, beta-blocker
Funding	Academic or government funding (Welsh Scheme for the Development of Health & Social Research, Welsh Heart Research Foundation, Flora Project, Health Reserach Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW FAT DIET versus USUAL DIET

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All death at 2 years; Group 1: 111/1018, Group 2: 113/1015; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD: MI at 2 years; Group 1: 35/1018, Group 2: 47/1016; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED OMEGA-3 FATTY ACID FISH DIET versus USUAL DIET

Protocol outcome 1: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD: MI at 2 years; Group 1: 49/1015, Group 2: 33/1018; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED OMEGA-3 FATTY ACID FISH DIET versus USUAL DIET FOR FISH DIET COMPARISION

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All death at 2 years; Group 1: 19/257, Group 2: 25/252; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED FIBRE DIET versus USUAL DIET

Protocol outcome 1: All-cause mortality at 10 years

- Actual outcome for Adults with established CVD: All death at 2 years; Group 1: 123/1017, Group 2: 101/1016; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Non-fatal myocardial infarction at 2 years; Group 1: 41/1017, Group 2: 41/1016; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study	**Burr 2003[251]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=3114)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 36 to 108 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: GP referral
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men treated for angina.
Exclusion criteria	Men who denied ever having exertional chest pain or discomfort, awaiting coronary artery by-pass surgery, already consuming 2 portions fish/week, unable to tolerate oily fish, unsuitable for other reasons (for example serious illness, anticipated to move out of area).
Recruitment/selection of patients	From GP practice.
Age, gender and ethnicity	Age - Mean (SD): Fish advice 61.0 (6.5) years, fruit advice 61.0 (6.5) years, no advice 61.2 (6.3) years. Gender (M:F): 452/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=764) Intervention 1: Diet intervention - Increased omega-3 fatty acid fish diet. Advice to consume at least 2 weekly portions of oily fish, or fish oil capsules if unable to tolerate fish. Duration 36 to 108 months. Concurrent medication/care: Beta-blockers (n=764) Intervention 2: Usual diet. Sensible eating. Duration 36 to 108 months. Concurrent medication/care: Beta blockers (n=779) Intervention 3: Diet intervention - Increased fruit and vegetables diet. Advice to eat 4-5 portions of fruit and

	vegetables, drink 1 glass of orange juice daily, increase intake of soluble fibre in the form of oats (8 g daily). Duration 36 to 108 months. Concurrent medication/care: Beta-blockers
Funding	Academic or government funding (British Heart Foundation, Seven Seas Limited, The Fish Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED OMEGA-3 FATTY ACID FISH DIET versus USUAL DIET Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All deaths at 36 to 108 months; Group 1: 141/764, Group 2: 109/764; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INCREASED FRUIT AND VEGETABLES DIET versus USUAL DIET Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All deaths at 36 to 108 months; Group 1: 133/779, Group 2: 109/764; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; Myocardial infarction at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study (subsidiary papers)	**Dayton 1969[389] (Dayton 1969[390])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=846)
Countries and setting	Conducted in USA; Setting: Domiciliary Unit.
Line of therapy	1st line
Duration of study	Intervention time: 8 years.
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged 54 years and above.
Exclusion criteria	None stated.
Recruitment/selection of patients	Volunteers.
Age, gender and ethnicity	Age - Other: Mean 65.5 years. Gender (M:F): 846/0. Ethnicity: Not reported.
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People aged over 75 years (Men aged 54 to 88 years). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=424) Intervention 1: Diet intervention - High polyunsaturated fat diet. Increased linoleic acid in diet and less saturated fat in diet provided. Duration 8 years. Concurrent medication/care: Not reported (n=422) Intervention 2: Usual diet. Usual diet provided. Duration 8 years. Concurrent medication/care: Not reported
Funding	Academic or government funding (Veterans Administration, Arthur Dodd Fuller Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years	

- Actual outcome: Definite cerebral infarction at 8 years; Group 1: 13/424, Group 2: 25/422; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome: Total death at 8 years; Group 1: 174/424, Group 2: 177/422; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome: Definite MI, overt or silent at 8 years; Group 1: 33/424, Group 2: 47/422; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 10 years - Actual outcome: Deaths due to acute atherosclerotic events at 8 years; Group 1: 48/424, Group 2: 70/422; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years-

Study (subsidiary papers)	**De lorgeril 1999[404] (De lorgeril m. 1994[400], De lorgeril 1997[401], De lorgeril 1999[405], De lorgeril 1996[402], De lorgeril 1998[403], Renaud 1995[1147])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=605)
Countries and setting	Conducted in France; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean 46 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG recording.
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	MI within 6 months of recruitment, aged < 70 years.
Exclusion criteria	Heart failure, hypertension recurrent angina, ventricular arrhythmia, atrioventricular block, other condition likely to limit long term survival or ability to participate in trial.
Recruitment/selection of patients	Consecutive.
Age, gender and ethnicity	Age - Mean (SD): Mediterranean diet group; 53.5 (10) years, usual diet group; 53.5 (10) years. Gender (M:F): 278/28. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Indirectness of population	No indirectness
Interventions	(n=302) Intervention 1: Diet intervention - Mediterranean diet. Mediterranean diet consisting of rapeseed oil or olive oil only oils allowed, more; bread, vegetables (root and green), fish, fruit every day, replace beef, lamb, and pork with poultry, no butter or cream. Duration Mean 46 months. Concurrent medication/care: Anticoagulants, antiplatelets, beta-blockers, calcium channel blockers, ACE inhibitors (n=303) Intervention 2: Usual diet. Usual diet. Duration Mean 46 months. Concurrent medication/care: Anticoagulants, antiplatelets, beta-blockers, calcium channel blockers, ACE inhibitors.

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDITERRANEAN DIET versus USUAL DIET Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults with established CVD: Stroke at 46 months; Group 1: 0/302, Group 2: 4/303; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause deaths at 46 months; Group 1: 14/302, Group 2: 24/303; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Non-fatal MI at 46 months; Group 1: 8/302, Group 2: 25/303; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study	**Estruch 2013**[479]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=7447)
Countries and setting	Conducted in Spain; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: Median 4.8 years (IQR 2.5 to 5.8)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Initial primary care physician identification. Verification at 2 screening visits of; clinical records and medical examination.
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men (aged 55-80 years), women (aged 60 to 80 years) with either type 2 diabetes or at least 3 of the following major risk factors; smoking, hypertension, elevated LDL-cholesterol levels, low HDL-cholesterol levels, overweight or obese, family history premature CAD.
Exclusion criteria	Cardiovascular disease (angina, MI, prior CABG/PCI, prior Q wave on ECG, stroke, TIA, PAD), severe medical condition impairing participation, HIV, drug use, alcoholism, food allergy / hypersensitivity, acute infection, other drug RCT participation, low predicted scoring of likelihood of adhering to diet, unable to follow diet for other reasons (for example, religious reasons), BMI > 40 kg/m2, institutionalised patients, inability to walk, no stable address, unable to attend 3 monthly clinics, illiteracy.
Recruitment/selection of patients	Recruited initially in primary care.
Age, gender and ethnicity	Age - Mean (SD): Mediterranean diet + olive oil group; mean (SD) 67.0(6.2) years, Mediterranean diet +nuts group; mean (SD) 66(6.2) years, usual diet group; mean (SD) 67.3(6.3) years. Gender (M:F): 3165/4282. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People aged over 75 years (Men; 55 to 80 years, women 50 to 80 years.). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Indirectness of population	No indirectness
Interventions	(n=2543) Intervention 1: Diet intervention - Mediterranean diet. Goal to consume 50 g or more of supplied polyphenol-rich olive oil/day, consumption of ≥ 2 daily servings of vegetables (at least 1 in a salad), ≥ 2-3 daily servings of fresh fruits (including natural juices), ≥ 3 weekly servings of legumes, ≥ 3 weekly servings of fish or seafood (at least 1 serving

	of fatty fish), ≥ 1 weekly serving of nuts or seeds, select white meats (poultry without skin or rabbit) instead of red meats or processed meats (burgers, sausages), cook at least twice a week with tomato, garlic and onion, limit the consumption of cream, butter, margarine, cold meat, pate, duck, carbonated and/or sugared beverages, pastries, industrial bakery products (cakes, donuts, or cookies), industrial desserts (puddings, custard), French fries or potato chips, and out-of-home pre-cooked cakes and sweets. Duration Median 4.8 years (IQR 2.5 to 5.8). Concurrent medication/care: Promotion of adherence by visits to dietician every 3 months where participants received individual counseling and group dietary training sessions, medical management in primary care (n=2454) Intervention 2: Diet intervention - Mediterranean diet. 30 g mixed nuts/day (15 g walnuts, 7.5 g walnuts, 7.5 d almonds) abundant olive oil, consumption of ≥ 2 daily servings of vegetables (at least 1 in a salad), ≥ 2-3 daily servings of fresh fruits (including natural juices), ≥ 3 weekly servings of legumes, ≥ 3 weekly servings of fish or seafood (at least 1 serving of fatty fish), ≥ 1 weekly serving of nuts or seeds, select white meats (poultry without skin or rabbit) instead of red meats or processed meats (burgers, sausages), cook at least twice a week with tomato, garlic and onion, limit the consumption of cream, butter, margarine, cold meat, pate, duck, carbonated and/or sugared beverages, pastries, industrial bakery products (cakes, donuts, or cookies), industrial desserts (puddings, custard), French fries or potato chips, and out-of-home pre-cooked cakes and sweets. Duration Median 4.8 years (IQR 2.5 to 5.8). Concurrent medication/care: Promotion of adherence by visits to dietician every 3 months where participants received individual counseling and group dietary training sessions, medical management in primary care (n=2450) Intervention 3: Usual diet. Participants advised to follow a low fat diet. Duration Median 4.8 years (IQR 2.5 to 5.8). Concurrent medication/care: Medical management in primary care
Funding	Academic or government funding (Biomedical Research Spanish Government, Instituto de Salud Carlos III, Centro de Investigacion Biomedica en Red de Fisiopatologia de la Obseidad y Nutricion, Centro Nacional de Investigaciones Cardiovasculares, Fondo de Investigacion Sanitaria-Fondo Europeo de Desarrollo Regional, Ministerio de Ciencia e Innovacion, Fundacion Mapfre 2010, Consejeria de Salud de la Junta de Andalucia, Public Health Division of the Dept. Health of Autonomous Government of Catalonia, Generalitat Valenciana, & Regional Government of Navarra)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDITERRANEAN DIET - EXTRA VIRGIN OLIVE OIL versus USUAL DIET Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults without established CVD: Stroke at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 49/2543, Group 2: 58/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years	

- Actual outcome for Adults without established CVD: Death from any cause at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 118/2434, Group 2: 114/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome for Adults without established CVD: Myocardial infarction at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 37/2543, Group 2: 38/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 10 years - Actual outcome for Adults without established CVD: Death from cardiovascular causes at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 26/2543, Group 2: 30/2450; Risk of bias: Low; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDITERRANEAN DIET - EXTRA NUTS versus USUAL DIET Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults without established CVD: Stroke at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 32/2454, Group 2: 58/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome for Adults without established CVD: Death from any cause at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 116/2454, Group 2: 114/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome for Adults without established CVD: Myocardial infarction at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 31/2454, Group 2: 38/2450; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 10 years - Actual outcome for Adults without established CVD: Death from cardiovascular causes at Median 4.8 years (IQR 2.5 to 5.8); Group 1: 31/2454, Group 2: 30/2450; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years-

Study	**Frantz 1989[512]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=9057)
Countries and setting	Conducted in USA; Setting: 6 state psychiatric hospitals and 1 nursing home.
Line of therapy	1st line
Duration of study	Intervention + follow up: 4.5 years.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: In-hospital psychiatric patients
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	People in psychiatric hospital.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Invitation in hospital.
Age, gender and ethnicity	Age - Other: Adults. Gender (M:F): 4393/4664. Ethnicity: Not reported.
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear (No age limit.). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: People with severe mental illness 7. Women: Male+female
Extra comments	Mean serum cholesterol level; 207 mg/dl. The average total time in hospital for each participant (including multiple admissions); 384 days. Hospital stays totaled 6005 days for high polyunsaturated fat diet group versus 5915 for usual diet group. Number of person years of observation was 9538, with 5903 of these for persons in the hospital continuously for > 2 years, and 2495 for > 4 years. Study does not state if any of the population had CV disease.
Indirectness of population	No indirectness
Interventions	(n=4541) Intervention 1: Diet intervention - High polyunsaturated fat diet. Increased polyunsaturated fatty acids to provide 18-20% of calories; limit saturated fat to < 9%, ratio polyunsaturated to saturated fat to > 2:1, cholesterol ≤ 150 mg/day. Duration 6005 days. Concurrent medication/care: Not reported (n=4516) Intervention 2: Usual diet. Usual diet provided by institution. Duration 5915 days. Concurrent medication/care: Not reported

	(n=2197) Intervention 3: Diet intervention - High polyunsaturated fat diet. Increased polyunsaturated fatty acids to provide 18-20% of calories; limit saturated fat to < 9%, ratio polyunsaturated to saturated fat to > 2:1, cholesterol ≤ 150 mg/day. Duration 6005 days. Concurrent medication/care: Not reported (n=2196) Intervention 4: Usual diet. Usual diet provided by institution. Duration 5915 days. Concurrent medication/care: Not reported (n=2344) Intervention 5: Diet intervention - High polyunsaturated fat diet. Increased polyunsaturated fatty acids to provide 18-20% of calories; limit saturated fat to < 9%, ratio polyunsaturated to saturated fat to > 2:1, cholesterol ≤ 150 mg/day. Duration 6005 days. Concurrent medication/care: Not reported (n=2320) Intervention 6: Usual diet. Usual diet provided by institution. Duration 5915 days. Concurrent medication/care: Not reported
Funding	Academic or government funding (National Heart, Lung & Blood Institute.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET

Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults without established CVD: Total stroke at 4.5 years; Group 1: 5/2197, Group 2: 8/2196; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome for Adults without established CVD: All deaths at 4.5 years; Group 1: 269/4541, Group 2: 248/4516; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET; MEN versus USUAL DIET; MEN

Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults without established CVD: Total stroke at 4.5 years; Group 1: 0/2197, Group 2: 4/2196; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome for Adults without established CVD: All deaths; men at 4.5 years; Group 1: 158/2197, Group 2: 153/2196; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET; WOMEN versus USUAL DIET; WOMEN

Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults without established CVD: All stroke; women at 4.5 years; Group 1: 5/2344, Group 2: 4/2320; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome for Adults without established CVD: All deaths; women at 4.5 years; Group 1: 111/2344, Group 2: 96/2330; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study (subsidiary papers)	**Leren 1966[834] (Leren 1967[835])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=412)
Countries and setting	Conducted in Norway; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG recording
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men post-MI.
Exclusion criteria	Diabetes, CV disease, syphilis, valvular heat disease, CKD, chronic lung disease, chronic rheumatic disease, cancer, muscular dystrophy, psychosis, depression, alcoholism, heart decompensation degree IV, known to be on cholesterol lowering diet.
Recruitment/selection of patients	From 13 medical units.
Age, gender and ethnicity	Age - Other: Increased polyunsaturated fat group mean age; 56.2 years versus usual diet group mean age; 56.3 years. Gender (M:F): 412/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: People withour severe mental illness 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=206) Intervention 1: Diet intervention - High polyunsaturated fat diet. Increased polyunsaturated fatty acids, total soy bean oil set at ½ litre per week, advice to restrict meat and remove fat, avoid whole milk, cream, butter, 1 egg permitted per week. Duration 5 years. Concurrent medication/care: Anticoagulant therapy and dietician gave continuous instruction and supervision including; home visits, letters and phone calls (n=206) Intervention 2: Usual diet. Usual diet. Duration 5 years. Concurrent medication/care: Anticoagulant therapy.
Funding	Other (Det Norske Rad for Hjerte- og karsyk-dommer, A/S Freia Chokoladefabriks, Arbeidsfond for Ernaerings-forskning,

	J.L. Tiedemannus, Tobaksfabrik, Joh. H Andresens me-disinske fond.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: Death at 5 years; Group 1: 48/206, Group 2: 66/206; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: CV mortality at 10 years - Actual outcome for Adults with established CVD: Total coronary death and stroke at 5 years; Group 1: 38/206, Group 2: 52/206; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Quality of life at 10 years-

Study (subsidiary papers)	**Ramsden 2013[1134] (Woodhill 1978[1446])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=459)
Countries and setting	Conducted in Australia; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG recording
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged between 30 to 59 years after recent coronary event; acute MI or angina.
Exclusion criteria	None reported.
Recruitment/selection of patients	Referred from a coronary clinic.
Age, gender and ethnicity	Age - Range: 30 to 59 years. Gender (M:F): 458/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=221) Intervention 1: Diet intervention - High polyunsaturated fat diet. Increase polyunsaturated fat intake to 15% total diet, reduce intake of saturated fatty acids and dietary cholesterol to less than 10%, participants provided with liquid safflower oil and safflower polyunsaturated margarine; individual education, diet assessed 3 times in first year and twice annually thereafter. Duration 5 years. Concurrent medication/care: Not reported (n=237) Intervention 2: Usual diet. Usual diet. Duration 5 years. Concurrent medication/care: Not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET	

Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 5 years; HR 1.62 (95%CI 1 to 2.64) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: CV mortality at 10 years - Actual outcome for Adults with established CVD: Cardiovascular mortality at 5 years; HR 1.7 (95%CI 1.03 to 2.8) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 5 years; Group 1: 38/221, Group 2: 27/237; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 10 years - Actual outcome for Adults with established CVD: Cardiovascular mortality at 5 years; Group 1: 37/221, Group 2: 26/237; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Quality of life at 10 years-

Study	**Rose 1965[1167]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=54)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG evidence of MI / WHO criteria
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	ECG evidence of infarction, or clear evidence of angina meeting WHO criteria, age < 70 years.
Exclusion criteria	Valvular disease, syphilis, anaemia, heart failure, non-cardiac disease likely to threaten life in 2 years, geographic / personal factors likely to interfere with clinic attendance or taking oil.
Age, gender and ethnicity	Age - Other: Mean age for corn oil diet group; 52.6 years, mean age for usual diet group 58.8 years. Gender (M:F): 54/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Diet intervention - High polyunsaturated fat diet. Corn oil supplement 80 g/day, advice to avoid fried foods, fatty meat, sausages, pastry, ice cream and cakes, milk, butter and eggs restricted, dietary follow-up 2 monthly. Duration 2 years. Concurrent medication/care: Conventional treatments (n=26) Intervention 2: Diet intervention - High polyunsaturated fat diet. Olive oil supplement 80 g/day, advice to avoid fried foods, fatty meat, sausages, pastry, ice cream and cakes, milk, butter and eggs restricted, dietary follow-up 2 monthly. Duration 2 years. Concurrent medication/care: Conventional treatments (n=26) Intervention 3: Usual diet. Usual diet. Duration 2 years. Concurrent medication/care: Conventional treatments

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET; CORN OIL versus USUAL DIET Protocol outcome 1: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Definite non-fatal MI at 2 years; Group 1: 3/28, Group 2: 3/26; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: CV mortality at 10 years - Actual outcome for Adults with established CVD: Sudden death at 2 years; Group 1: 3/28, Group 2: 1/26; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; Quality of life at 10 years-

Study	**Singh 1991**[1271]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=463)
Countries and setting	Conducted in India; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Unclear description of population.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	With and without atheromatous diseases.
Exclusion criteria	Cancer, CKD, diarrhea, dysentry, did not like the diet.
Recruitment/selection of patients	Study dietician recruited people from local newspapers, clubs and clinics.
Age, gender and ethnicity	Age - Mean (SD): High polyunsaturated fat group; 45.2 (9.5) years versus usual diet group 47.5 (11.2) years. Gender (M:F): 414/44. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian (Study conducted in India). 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Indirectness of population	Serious indirectness: Unclear population; CVD versus non CVD
Interventions	(n=228) Intervention 1: Diet intervention - High polyunsaturated fat diet. Increase polyunsaturated fat intake by replacing meat and eggs with following to ensure diet isocaloric, fish or protein, fat rich cereals, cottage cheese. Duration 1 year. Concurrent medication/care: Not reported (n=230) Intervention 2: Usual diet. Usual diet. Duration 1 year. Concurrent medication/care: Medical management not reported
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH POLYUNSATURATED FAT DIET versus USUAL DIET	

Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome: Stroke at 1 year; Group 1: 1/228, Group 2: 3/230; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome: Deaths at 1 year; Group 1: 8/228, Group 2: 11/230; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome: Non-fatal MI at 1 year; Group 1: 4/228, Group 2: 10/230; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study	**Singh 2002[1269]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1000)
Countries and setting	Conducted in India; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	MI or 1 or more of the following risk factors for CAD; hypertension, hypercholesterolemia, diabetes, angina.
Exclusion criteria	Cancer, chronic diarrhea or dysentery, blood urea > 6.6 mmol/l, arthritis, dislike of intervention diet, refusal of laboratory testing.
Recruitment/selection of patients	Recruited through advertisements in newspapers and local service clubs.
Age, gender and ethnicity	Age - Mean (SD): Indo-Mediterranean diet; 49 (10) years, usual diet; 48 (9) years. Gender (M:F): 897/103. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Indirectness of population	No indirectness
Interventions	(n=499) Intervention 1: Diet intervention - Mediterranean diet. Indo-Mediterranean diet; 400-500 g vegetables, fruits and nuts/day, 400-500 g whole grains, legumes, rice, maize and wheat, mustard seed or soy bean oil in 3-4 servings/day. Duration 2 years. Concurrent medication/care: Appropriate drugs for angina, arrhythmias, hypertension, diabetes, information on diet given by dietician at each visit to clinic (n=501) Intervention 2: Usual diet. Usual diet. Duration 2 years. Concurrent medication/care: Appropriate drugs for angina, arrhythmias, hypertension, diabetes, information on prudent diet given by dietician at each visit to clinic
Funding	Academic or government funding (Centre of Nutrition and Heart)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDITERRANEAN DIET versus USUAL DIET

Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years
- Actual outcome: Stroke at 2 years; Group 1: 7/499, Group 2: 13/501; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome: Total deaths at 2 years; Group 1: 24/499, Group 2: 38/501; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Myocardial infarction at 10 years
- Actual outcome: Non-fatal MI at 2 years; Group 1: 21/499, Group 2: 43/501; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years-

Study	**Watts 1992[1417]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in United Kingdom; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Coronary angiography.
Stratum	Adults with established CVD:
Subgroup analysis within study	Not applicable: Not applicable
Inclusion criteria	Men with prior MI and / or angina, < 66 years, plasma cholesterol concentration > 6.0 mmol/l.
Exclusion criteria	Plasma triglyceride concentrations > 4 mmol/l, cholesterol > 10 mmol/l, fasting glucose > 7 mmol/l, cardiac failure, MI within previous 8 weeks, malignancy, other major organ failure, accelerated hypertension, requiring revascularisation.
Recruitment/selection of patients	Referral for coronary angiography.
Age, gender and ethnicity	Age - Other: Low fat diet, mean (SE); 48.9 (1.6) years versus usual diet, mean (SE); 53.9 (1.6) years. Gender (M:F): 55/0. Ethnicity: Not given
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Diet intervention - Low fat diet. Total fat reduced to 27% of total dietary energy; saturated fatty acid content 8 - 10% of dietary energy, dietary cholesterol 100 mg/1000 kcal, omega-3 and omega-6 polyunsaturated fatty acid increased to 8% of dietary energy, plant-derived soluble fibre (chiefly pectin) intake increased to the equivalent of 3.8 g polygalacturonate / 1000 kcal. Duration 3 years. Concurrent medication/care: Beta-blockers, calcium antagonists, long acting oral nitrates, diuretics, aspirin, dipyridamole. Dietetic assessment of diet and advice (n=28) Intervention 2: Usual diet. Usual diet. Duration 3 years. Concurrent medication/care: Beta-blockers, calcium antagonists, long acting oral nitrates, diuretics, aspirin, dipyridamole

Funding	Study funded by industry (Unilever plc, the Chemical Pathology Fund of St Thomas' Hospital, Bristol Myers)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW FAT DIET versus USUAL DIET Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults with established CVD: Stroke at 3 years; Group 1: 0/27, Group 2: 1/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: Deaths at 3 years; Group 1: 1/27, Group 2: 3/28; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Myocardial infarction at 3 years; Group 1: 1/27, Group 2: 2/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 10 years - Actual outcome for Adults with established CVD: CV deaths at 3 years; Group 1: 1/27, Group 2: 3/28; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years-

G.3 Foods enriched with phytosterols (plant stanols and sterols)

None

G.4 Efficacy of statin therapy

Study (subsidiary papers)	**Amarenco 2006[83] (Briel 2004[216], Amarenco 2007[86], Goldstein 2008[569], Goldstein 2009[570], Amarenco 2010[85])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4731)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TIA diagnosed by a neurologist within 30 days after the event. Stroke was defined by focal clinical signs of central nervous system dysfunction of vascular origin that lasted for at least 24 hours; TIA was defined by the loss of cerebral or ocular function for less than 24 hours, presumably owing to arthersclerotic causes.
Stratum	Adults with established CVD : Men and women with a history of stroke or transient ischaemic attack
Subgroup analysis within study	Post-hoc subgroup analysis: Post-hoc subgroup analysis was conducted in groups of patients who achieved different levels in reduction of LDL-cholesterol from baseline (Amarenco et al. 2007b), by baseline stroke subtypes (Amarenco et al. 2010), and by the severity of the index stroke (Goldstein et al. 2009), and by sex (Goldstein et al. 2008b)
Inclusion criteria	Men and women over 18 years of age who had an ischemic or haemorrhagic stroke or a TIA, 1 to 6 months before randomisation. Patients with haemorrhagic stroke were included if they were deemed by the investigator to be at risk ischemic stroke or CHD. Patients had to be ambulatory, with a modified Rankin score of no more than 3, and to have an

	LDL cholesterol level of at least 100 mg/dL and no more than 190 mg/dL.
Exclusion criteria	Atrial fibrillation, other cardiac sources of embolism, and subarachnoid haemorrhage.
Recruitment/selection of patients	Patients were enrolled between Sept 1998 and March 2001.
Age, gender and ethnicity	Age - Other: Atorvastatin 63 (SE 0.2) years, placebo 62.5 (SE 0.2). Gender (M:F): 60%/40%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Patients who were taking lipid-altering drugs had to stop these medications 30 days before the screening phase of the study. Baseline total cholesterol (mg/dL): mean (SE) 211.4 (0.6) in atorvastatin group and 212.3 (0.6) in the placebo group; LDL-cholesterol (mg/dL: mean (SE) 132.7 (0.5) in atorvastatin group and 133.7 (0.5) in the placebo group. After treatment: total cholesterol (mg/dL): mean (SE) 147.2 (0.6) in atorvastatin group and 208.4 (0.6) in the placebo group; LDL-cholesterol (mg/dL): mean (SE) 72.9 (0.5) in atorvastatin group and 128.5 (SE 0.5) in the placebo group. The percentage of people with diabetes at baseline was not reported; 69% had a stroke, and 31% had a TIA.
Indirectness of population	No indirectness
Interventions	(n=2365) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration Median 4.9 years. Concurrent medication/care: Dietary advice (NCEP Step 1); 2% had received a prior statin therapy. After randomisation, the following % of patients were aspirin or other antiplatelet drug (excluding heparin): 94%; ACE inhibitor: 47%; dihydropyridine derivative: 28%; beta blocker: 32%; ARBs: 14%; vitamin K antagonist (including warfarin): 12% (n=2366) Intervention 2: Placebo. Placebo. Duration Median 4.9 years. Concurrent medication/care: Dietary advice (NCEP Step 1); 3% had received a prior statin therapy. After randomisation, the following % of patients were taking aspirin or other antiplatelet drug (excluding heparin): 94%; ACE inhibitor: 47%; dihydropyridine derivative: 30%; beta blocker: 33%; ARBs: 15%; vitamin K antagonist (including warfarin): 12%, or open-label statins: 25%
Funding	Study funded by industry (Supported by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke (fatal and non-fatal) at Median 4.9 years; Group 1: 265/2365, Group 2: 311/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Stroke (fatal and non-fatal) at Median 4.9 years; HR 0.84 (95%CI 0.71 to 0.99) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at Median 4.9 years; Group 1: 2/2365, Group 2: 3/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at Median 4.9 years; Group 1: 216/2365, Group 2: 211/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : All-cause mortality at Median 4.9 years; HR 1 (95%CI 0.82 to 1.21) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from cardiovascular disease at Median 4.9 years; Group 1: 78/2365, Group 2: 98/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Death from cardiovascular disease at Median 4.9 years; HR 0.78 (95%CI 0.58 to 1.06) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at Median 4.9 years; Group 1: 129/2365, Group 2: 141/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Alanine or aspartate aminotransferase > 3 times the upper limit of the normal group on 2 occasions at Median 4.9 years; Group 1: 51/2365, Group 2: 11/2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 7: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at Median 4.9 years; Group 1: mean 1.89 mmol/l (SD 0.62); n=2365, Group 2: mean 3.32 mmol/l (SD

0.75); n=2366; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Anderssen 2005[92]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=568)
Countries and setting	Conducted in Unknown; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Hypertensive males
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged 40-74 years receiving drug treatment for hypertension, total cholesterol 4.5-8.0 mmol/l, triglycerides <4.5 mmol/l, BMI 25-35kg/m², and sedentary lifestyle (<1h per week of regular exercise).
Exclusion criteria	Symptomatic CVD (MI, angina pectoris, stroke), CHF, type 1 diabetes mellitus, history of coronary intervention, need for treatment with lipid-lowering medications other than the study drug, known or suspected hepatic or renal impairment or malignancy, history of alcohol and/or drug abuse, vegetarian diet or diet comprising a high omega-3 fatty acid intake, and inability to perform physical exercise.
Age, gender and ethnicity	Age - Mean (SD): Fluvastatin alone 56.8 (8.6) years, placebo alone 57.7 (8.2) years, fluvastatin and lifestyle 57.9(8.7) years, placebo and lifestyle 56.4 (9.1) years. Gender (M:F): 568/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).

Extra comments	2x2 Factorial study design with patients being randomised twice to fluvastatin versus placebo and then lifestyle interventions versus usual care. Baseline total cholesterol mean (SD); fluvastatin 5.84 (0.75), placebo 5.95 (0.93), fluvastatin and lifestyle 6.02 (0.85), placebo and lifestyle 5.99 (0.90). Three month total cholesterol reduction; fluvastatin 5.93 to 5.01 mmol/l. Baseline LDL-cholesterol mean (SD); fluvastatin 3.78 (0.7), placebo 3.86 (0.86), fluvastatin and lifestyle 3.97 (0.82), placebo and lifestyle 3.91 (0.78). Three month LDL-cholesterol fluvastatin reduction 3.87 to 3.02 mmol/l.
Indirectness of population	No indirectness
Interventions	(n=283) Intervention 1: Low intensity statin - Fluvastatin 40 mg. Fluvastatin 40 mg/day (Lescol, Novartis Pharma). Duration 4 years. Concurrent medication/care: Calcium antagonists 37%, beta blockers 19%, diuretics 28%, ACE inhibitors 31% Comments: Group includes Fluvastatin alone (142) plus Fluvastatin with lifestyle intervention (141) (n=285) Intervention 2: Placebo. Placebo. Duration 4 years. Concurrent medication/care: Calcium antagonists 40%, beta blockers 22%, diuretics 26%, ACE inhibitors 31% Comments: Group includes Placebo alone plus Placebo with lifestyle interventions
Funding	Study funded by industry (Novartis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis (CK>10 times normal) at 4 years; Group 1: 0/283, Group 2: 1/285; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Mortality at 4 years; Group 1: 4/283, Group 2: 5/285; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years;

	Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Anon 1994[12] (Pyorala 1997[1117])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4444)
Countries and setting	Conducted in Denmark, Norway, Sweden; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5.4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with CHD (angina pectoris or MI)
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, age 35-70; history of angina pectoris or acute MI; serum total cholesterol >5.5 mmol/l.
Exclusion criteria	Premenopausal women of childbearing potential; secondary hypercholesterolaemia; unstable or Prinzmetal angina; tendon xanthomata; planned coronary artery surgery or angioplasty; MI during the preceding 6 months; anti arrhythmic therapy; CHF requiring treatment with digitalis, diuretics, or vasodilators; persistent atrial fibrillation; cardiomegaly, haemodynamically important valvular heart disease; history of completed stroke; impaired hepatic function; partial ileal bypass; history of drug or alcohol abuse; poor mental function; other serious disease; current treatment with another investigational drug, or hypersensitivity to HMG-CoA reductase inhibitors.
Recruitment/selection of patients	Recruited from 94 Scandinavian clinical centres.
Age, gender and ethnicity	Age - Mean (SD): Placebo men: 58.1 (7.2) years; placebo women: 60.51 (5.7) years; simvastatin men: 58.2 (7.3) years; simvastatin women: 60.5 (6.4) years. Gender (M:F): 3617/827. Ethnicity: Not stated (assumed white)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline values, mean (SD) (mmol/l) total cholesterol: placebo: 6.75 (0.66), simvastatin: 6.75 (0.67). LDL-cholesterol: placebo: 4.87 (0.65), simvastatin: 4.87 (0.66).
Indirectness of population	No indirectness
Interventions	(n=2221) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Target treatment was total cholesterol 3.0-5.2 mmol/l. 37% of patients had their dose raised to 40 mg/day during the first 6 months after randomisation. 2 patients had their dose reduced to 10 mg/day. Duration 5.4 years. Concurrent medication/care: Aspirin: 37%; beta blockers: 57%; calcium antagonist: 32%; isosorbide mono/dinitrate: 31%; thiazides: 7%; warfarin: 1%; fish oil: 13% (n=2223) Intervention 2: Placebo. Matching placebo. 35 patients were switched to lipid-lowering drugs, either because total cholesterol rose above the protocol-specified limit of 9.0 mmol/l (16 patients) or because such therapy was initiated by non-study physicians (19 patients). Duration 5.4 years. Concurrent medication/care: Aspirin: 37%; beta blockers: 57%; calcium antagonist: 30%; isosorbide mono/dinitrate: 33%; thiazides: 6%; warfarin: 2%; fish oil: 13%
Funding	Study funded by industry (Merck Research Laboratories, Rahway, New Jersey, USA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Definite acute MI at 5.4 years; Group 1: 164/2221, Group 2: 270/2223; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Non-fatal definite MI (diabetes subgroup) at 5.4 years; Group 1: 7/105, Group 2: 24/97; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Any cerebrovascular event at 5.4 years; Group 1: 61/2221, Group 2: 95/2223; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 5.4 years; Group 1: 1/2221, Group 2: 0/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : CK >10 times ULN at 5.4 years; Group 1: 6/2221, Group 2: 1/2223; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 5.4 years; Group 1: 182/2221, Group 2: 256/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: All-cause mortality (diabetes subgroup) at 5.4 years; Group 1: 15/105, Group 2: 24/97; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 5.4 years; HR 0.7 (95%CI 0.58 to 0.85) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 5.4 years; Group 1: 136/2221, Group 2: 207/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with type 2 diabetes: CV mortality (diabetes subgroup) at 5.4 years; Group 1: 12/105, Group 2: 20/97; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : AST >3 times ULN at 5.4 years; Group 1: 20/2221, Group 2: 23/2223; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : ALT >3 times ULN at 5.4 years; Group 1: 49/2221, Group 2: 33/2223; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 5.4 years; Group 1: 198/2116, Group 2: 193/2126; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Anon 1998[16] (White 2000,[1427] Hunt 2001,[686] Marschner 2001,[921] Simes 2002,[1258] Hague 2003,[605] Keech 2003[745])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=9014)
Countries and setting	Conducted in Australia, New Zealand; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 8 years (6 years intervention)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Men and women with CHD and a broad range of cholesterol levels
Subgroup analysis within study	Stratified then randomised: Stratified according to the qualifying event (MI or unstable angina) and clinical centre
Inclusion criteria	Patients after acute MI or a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry. After patients entered a 8 week single-blind run-phase of dietary advice, their plasma total cholesterol level had to be between 155-271 mg/dL and the fasting triglyceride level less than 445 mg/dL 4 weeks before randomisation to qualify for the trial.
Exclusion criteria	Clinically significant medical or surgical event within 3 months before study entry, cardiac failure, renal or hepatic disease, and the current use of any cholesterol-lowering agents.
Recruitment/selection of patients	Patients were recruited from 87 centres; patients entered an 8-week long single-blind placebo run-in phase during which they received dietary advice aimed at reducing their fat intake to less than 30% of total energy intake; patients were randomised between June 1990 and December 1992.
Age, gender and ethnicity	Age - Median (range): 62 (55-68) years. Gender (M:F): 83%/17%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD:

	Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline total cholesterol mg/dL, median (IQR): 218 (196-241) pravastatin, 218 (196-240) placebo; LDL-cholesterol mg/dL, median (IQR): 150 (130-170) pravastatin, 150 (131-170) placebo; at the end of treatment: 179 mg/dL pravastatin (the authors stated that this was 18% points greater than in the placebo group (p<0.001), but did not report the final value in the placebo group); the authors also reported that LDL-cholesterol was reduced by 25% more in the pravastatin group than the placebo group (actual values were not reported). Participants with diabetes mellitus: 9%; participants with MI at baseline: 64%; participants with stroke at baseline: 4%.
Indirectness of population	No indirectness
Interventions	(n=4512) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 6.1 years. Concurrent medication/care: Dietary advice (no further details reported) (n=4502) Intervention 2: Placebo. Placebo. Duration 6.1 years. Concurrent medication/care: Dietary advice (no further details reported)
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Any MI (not clear if all non-fatal) at 6.1 years; Group 1: 366/4512, Group 2: 463/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : MI (not clear if all non-fatal) at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 435/4512, Group 2: 570/4502; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Any stroke at 6.1 years; Group 1: 169/4512, Group 2: 204/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Stroke at 6.1 years; Group 1: 34/542, Group 2: 53/535; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Total stroke at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 224/4512, Group 2: 272/4502;

Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 6.1 years; Group 1: 498/4512, Group 2: 633/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Death from any cause at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 717/4512, Group 2: 888/4502; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 6.1 years; HR 0.82 (95%CI 0.73 to 0.92) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death due to cardiovascular disease at 6.1 years; Group 1: 331/4512, Group 2: 433/4502; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Death due to cardiovascular disease at 8 years (6 years intervention + 2 years open label pravastatin) ; Group 1: 461/4512, Group 2: 596/4502; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 6.1 years; Group 1: 126/3496, Group 2: 138/3501; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Anon 2000[21]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4271)
Countries and setting	Conducted in Italy; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: mean 23 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable:
Inclusion criteria	6 months post-acute MI; stable post-infarction clinical condition; stable plasma cholesterol levels between 200 and 250 mg/dL or >250mg/dL if this alone not a sufficient reason for treating the patient (absence of other risk factors).
Exclusion criteria	Contraindications to study treatments; comorbid conditions indicating an unfavourable survival prognosis over a short period of time (for example, malignancy); mental of physical disorders substantially affecting patients compliance; known congenital coagulation defects, known hepatic diseases, renal diseases with serum creatinine ≥3.5mg/dL; presence of other conditions requiring cholesterol-lowering treatment (for example, hypertriglyceridemia ≥500mg/dL); diseases requiring cyclosporine treatment.
Recruitment/selection of patients	Population recruited from cohort of patients randomised to different cholesterol-lowering regimens (n-3 polyunsaturated fatty acids versus vitamin E versus combination versus standard treatment).
Age, gender and ethnicity	Age - Mean (SD): Pravastatin 59.7 (10.4) years, control 60.0 (10.4) years. Gender (M:F): 3684/587. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mmol/l; pravastatin 5.94, control 5.92, total cholesterol at 2 years; pravastatin 5.35, control 5.82. Baseline LDL-cholesterol mmol/l; pravastatin 3.93, control 3.92, LDL cholesterol at 2 years; pravastatin 3.34, control 3.8. Diabetes mellitus; pravastatin 12.9%, control 14.4%. Modifications of study protocol in February 1995 (2 years in to study) - patients with total cholesterol >250mg/dL no longer randomised, patients already randomised with total cholesterol >250mg/dL offered cholesterol lowering therapy if not contraindicated, lower cut-off level of 200mg/dL abolished. In December 1996 trial stopped due to ethical and practical reasons following results of CARE trial.
Indirectness of population	No indirectness
Interventions	(n=2138) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 20 mg/day. Dose increased to 40 mg for 4.1% of intervention group, dose reduced to 10 mg for 3.1% of intervention group, adjunctive cholesterol-lowering drug prescribed for 2.2% of intervention group. Duration mean 23 months. Concurrent medication/care: Secondary prevention post-MI. Concomitant treatment: n-3 PUFA 50.1%, vitamin E 49.8%, aspirin 79.8%, other antiplatelet therapy 13.5%, beta blockers 42.7%, calcium antagonists 32.2%, ACE inhibitors 40.2%, nitrates 59.0%, diuretics 10.1% (n=2133) Intervention 2: Placebo. No treatment. Duration mean 23 months. Concurrent medication/care: Secondary prevention post-MI. Concomitant treatment: n-3 PUFA 50.3%, vitamin E 49.1%, aspirin 77.8%, other antiplatelet therapy 13.3%, beta blockers 43.2%, calcium antagonists 32.1%, ACE inhibitors 42.8%, nitrates 59.0%, diuretics 10.8%
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO Protocol outcome 1: Non-fatal MI at 5 years - Actual outcome for Adults with established CVD : Non-fatal MI (probable and definite) at 23 months; Group 1: 39/2138, Group 2: 41/2133; Risk of bias: High; Indirectness of outcome: No indirectness	

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke (probable and definite) at 23 months; Group 1: 16/2138, Group 2: 15/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All fatal events at 23 months; Group 1: 72/2138, Group 2: 88/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : CV mortality at 23 months; Group 1: 52/2138, Group 2: 65/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Muscular pain or weakness at 23 months; Group 1: 6/2138, Group 2: 0/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 23 months; Group 1: 15/2138, Group 2: 0/2133; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:New onset diabetes at 5 years
- Actual outcome for Adults with established CVD : New onset diabetes at 23 months; Group 1: 96/1743, Group 2: 105/1717; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Anon 2002[25] (Margolis 2009[916])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=10,355)
Countries and setting	Conducted in Canada, Puerto Rico, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 4.8 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fasting lipid profiles and ECG
Stratum	Adults without established CVD : Men and women with hypertension and at least 1 other CHD risk factor
Subgroup analysis within study	Stratified then randomised: Stratified by centre and antihypertensive treatment arm
Inclusion criteria	Prior enrollment in ALLHAT RCT (age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting LDL-cholesterol level of 120 to 189 mg/dL for those with no known CHD, or 100 to 129 mg/dL for those with known CHD; and fasting triglyceride levels lower than 350 mg/dL.
Exclusion criteria	Participants currently receiving lipid-lowering therapy, taking large doses of niacin, or taking probucol in the last year; were known to be intolerant of statins or to have significant liver or kidney disease or contraindications for statin therapy; or had a known secondary cause of hyperlipidemia.
Recruitment/selection of patients	Participants were drawn exclusively from ALLHAT, a 4-armed antihypertensive trial,recuited from 513 clinical centres, enrollment took place from March 1994 though to May 1998.
Age, gender and ethnicity	Age - Mean (SD): Pravastatin 66.4 (7.6) years, usual care 66.3 (7.5) yeras. Gender (M:F): 51%/49%. Ethnicity: 41% White; 34% Black; 19% Hispanic; 6% other
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean (SD) pravastatin; 223.7 (26.9), usual care; 223.7 (26.7). Baseline LDL-cholesterol (mg/mL): mean (SD) pravastatin; 145.6 (21.4), placebo; 145.5 (21.3). At year 4 total cholesterol: mean (SD) pravastatin; 184.3 (35.3), control; 205.9 (36.6). At year 6 total cholesterol: mean (SD) pravastatin; 177.6 (33.8), control; 196.5 (37.3). At year 4 LDL-cholesterol: mean (SD) pravastatin; 104.5 (28.1), control; 128.7 (32.6). At year 6 LDL-cholesterol: mean (SD) pravastatin 104.0 (29.1), control; 121.2 (34.6). People with type 2 diabetes: 35%; people with a history of CHD: 14%.
Indirectness of population	No indirectness
Interventions	(n=5170) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Initially pravastatin participants began with a dosage of 20 mg taken each evening and increased to 10 mg/day as needed to achieve at least a 25% decrease in LDL-cholesterol. After the first 1000 participants had been enrolled, an uniform dosage of 40 mg/day was adopted. Study practitioners retained the option to lower the dose of pravastatin, or discontinue the drug if significant adverse effects occurred. Duration Mean 4.8 years. Concurrent medication/care: Dietary advice (NCEO Step I diet); study practitioners could prescribe other lipid-lowering interventions, including cholesterol-lowering drugs not supplied by the study (n=5185) Intervention 2: Placebo. Usual care; treated for LDL-cholesterol lowering according to the discretion of a participant's primary care physician, although vigorous cholesterol-lowering therapy in the usual care group was discouraged unless warranted by a change in clinical circumstances. Duration Mean 4.8 years. Concurrent medication/care: Dietary advice (NCEP Step I diet)
Funding	Equipment / drugs provided by industry (Supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute. Bristol-Myers Squibb supplied pravastatin, and financial support was also provided by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults without established CVD : Non-fatal stroke at 6 years; Group 1: 156/5170, Group 2: 175/5185; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at 6 years; Group 1: 631/5170, Group 2: 641/5185; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years
- Actual outcome for Adults without established CVD : CV mortality at 6 years; Group 1: 295/5170, Group 2: 300/5185; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults without established CVD : Alanine transaminase >3 times the upper limit of normal at 6 years; Group 1: 21/5170, Group 2: 0/5185; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event:New onset diabetes at 5 years
- Actual outcome for Adults without established CVD : New onset diabetes at 6 years; Group 1: 238/3017, Group 2: 212/3070; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults without established CVD : LDL-cholesterol at 6 years; Group 1: mean 4.77 mmol/l (SD 0.91); n=5170, Group 2: mean 5.32 mmol/l (SD 0.95); n=5185; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Armitage 2010[107] (Bowman 2007[205])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=12064)
Countries and setting	Conducted in United Kingdom; Setting: SEARCH trial. 88 UK hospitals
Line of therapy	1st line
Duration of study	Intervention time: Mean (SD): 6.7 years (1.5)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-80 years; history of previous MI; current statin use or clear indication for this treatment (and no clear indication for folic acid); total-C ≥3.5 mmol/l if already on statin or ≥4.5 mmol/l if not; no clear contraindications to the study treatment
Exclusion criteria	Predominant medical problems that could reduce compliance with long-term study treatment.
Recruitment/selection of patients	Pre-randomisation run-in phase: simvastatin 20 mg/day (and placebo vitamins) and instructed to stop taking any non-study statin.
Age, gender and ethnicity	Age - Mean (SD): 64 (9) years. Gender (M:F): 10012/2052. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline values (mmol/l): total-C: 4.23 (0.73); LDL-C: 2.50 (0.61). Average mean differences (SE) for simva 80 minus simva 20: total-C: -0.40 (0.01); LDL-C: -0.35 (0.01).
Indirectness of population	No indirectness
Interventions	(n=6033) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 6.7 years. Concurrent medication/care: Aspirin (or another antiplatelet) 91%; warfarin: 5%; beta blocker: 48%; nitrate: 44%; calcium channel blocker: 27%; ACE inhibitor: 38%; angiotensin II receptor antagonist: 4%; hypoglycemics (oral or insulin): 8% (n=6031) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg/day. Duration 6.7 years. Concurrent medication/care: Aspirin (or another antiplatelet) 91%; warfarin: 5%; beta blocker: 48%; nitrate: 44%; calcium channel blocker: 27%; ACE inhibitor: 38%; angiotensin II receptor antagonist: 4%; hypoglycemics (oral or insulin): 8%
Funding	Study funded by industry (Merck, UK Medical Research Council, British Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 6.7 years; Group 1: 463/6033, Group 2: 397/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 6.7 years; Group 1: 230/6033, Group 2: 209/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Definite rhabdomyolysis at 6.7 years; Group 1: 0/6033, Group 2: 7/6031; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : 10<CK≤40 ULN at 6.7 years; Group 1: 12/6033, Group 2: 45/6031; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 6.7 years; Group 1: 970/6033, Group 2: 964/6031; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Any vascular death at 6.7 years; Group 1: 572/6033, Group 2: 565/6031; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New diabetes at 6.7 years; Group 1: 591/6033, Group 2: 633/6031; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Asselbergs 2004[113] (Asselbergs 2005[114])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=864)
Countries and setting	Conducted in Netherlands; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: mean 46 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hospitalisation values for blood pressure and cholesterol were based on guidelines of GPs from the Netherlands in 1998; outcome measures were reported in detail
Stratum	Adults with CKD: Men and women with microalbuminuria (with a low prevalance of diabetes mellitus, and low prevalence of previous CV event; also normal blood pressure and cholesterol level at baseline)
Subgroup analysis within study	Post-hoc subgroup analysis: High and low albuminuria
Inclusion criteria	Participants in the PREVEND IT had to have persistent microalbuminuria, a blood pressure <160/100 mm Hg and no use of hypertensive medicine, and a total cholesterol level <8.0 mmol/l, or <5.0 nmol/l in case of previous MI, and no use of lipid-lowering medication
Exclusion criteria	Creatinine clearance <60% of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptor antagonists.
Recruitment/selection of patients	PREVEND IT is a substudy of the PREVEND program (a program to assess the value of microalbinuria as an indicator of increased cardiovascular and renal risk in the general population). In 1997 to 1998, all inhabitants (28 to 75 years) of the city of Groningen were asked to send in a morning urine sample, and to fill out a questionnaire. From April 1998 to June 1999, subjects willing to participate in PREVENT IT
Age, gender and ethnicity	Age - Mean (SD): 51 (12) years. Gender (M:F): 65%/35%. Ethnicity: 95-97% 'White'

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mmol/l): mean (SD) 5.8 (1.1) (in both treatment groups); LDL-cholesterol: 4.1 ((1.0) pravastatin and 4.0 (1.0) placebo; At 4 years total cholesterol: 4.8 (1.0) (n=376) pravastatin group and 5.6 (1.1) (n=382) in the placebo group; LDL-cholesterol: 3.1 (0.9) (n=375) in the pravastatin group and 3.9 (0.9) (n=379) in the placebo group; Baseline data: 2.8% in active and 2.3% had diabetes mellitus; 0.2% in active and 0.7% in placebo had MI; 4.4% in active and 2.3% in placebo group had a prior CV event.
Indirectness of population	No indirectness
Interventions	(n=433) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration Mean 46 months. Concurrent medication/care: Some of the participants also received fosinopril 20 mg (n=431) Intervention 2: Placebo. Placebo. Duration Mean 46 months. Concurrent medication/care: Some of the participants also received fosinopril 20 mg
Funding	Academic or government funding (Funded by a grant from the Dutch Kidney Foundation and the Netherlands Heart Foundation, and an unrestricted grant from Bristol Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with CKD: Hospitalisation for nonfatal myocardial infarction and/or myocardial ischaemia at 46 months; Group 1: 8/433, Group 2: 15/431; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with CKD: Cerebrovascular accident at 46 months; Group 1: 7/433, Group 2: 4/431; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults with CKD: Cardiovascular mortality at 46 months ; Group 1: 4/433, Group 2: 4/431; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with CKD: LDL-cholesterol at 46 months ; Group 1: mean 3.1 mmol/l (SD 0.9); n=433, Group 2: mean 3.9 mmol/l (SD 0.1); n=431; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Athyros 2002[120] (Athyros 2005,[118] Athyros 2007[117])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1,600)
Countries and setting	Conducted in Greece; Setting: Conducted in out-patient clinics or usual care outside of the hospital.
Line of therapy	1st line
Duration of study	Intervention time: Mean 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CHD defined as a history of prior MI or >70% stenosis of least 1 coronary artery, as documented by a coronary angiogram.
Stratum	Adults with established CVD : Men and women with established coronary heart disease
Subgroup analysis within study	Post-hoc subgroup analysis: Subgroup analysis was conducted in women, patients with diabetes mellitus, arterial hypertension, age 60-75 years, congestive heart failure, recent unstable angina or prior revascularisation. In addition, analyses were conducted in patients with coronary heart disease and metabolic syndrome (Athyros et al. 2007), and combined treatment with a statin plus low dose ASA compared with each drug alone or neither drug (Athyros et al. 2005)
Inclusion criteria	Patients <75 years with established CHD; LDL cholesterol >100 mg/dL and triglycerides <400 mg/dL. There was no other limit in lipid profile values. Patients with recent ACS were not excluded.
Exclusion criteria	Renal or liver dysfunction, prior hypolipidaemic treatment, childbearing potential and any significant disease likely to limit life to less than the duration of the study (for example, malignancies and heart failure NYHA class II or IV). Patients that were scheduled for coronary revascularisation were also excluded. Patients with liver enzyme increase more than 3-fold ULN, creatine kinase 5 to 10 times ULN, or myalgia without serum creatine kinase elevation would be removed from the study.
Recruitment/selection of patients	Consecutive patients were randomised over a 2-year period; all patients with a LDL-cholesterol >100 mg/dL after a 6-week period on hypolidaemic diet (NCEP step 2) were enrolled into the study.

Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 58 (2) years, usual care 59 (14) years. Gender (M:F): 79%/21%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean 257 (SD) (39) in atorvastatin group and 255 (37) in the usual care group; LDL-cholesterol (mg/dL): mean (SD) 180 (27) in atorvastatin group and 179 (28) in usual care group. After treatment: total cholesterol (mg/dL): mean (SD) 165 (10) in atorvastatin group and 245 (41) in the usual care group; LDL-cholesterol (mg/dL): mean (SD) 97 (4) in atorvastatin group and 169 (32) in usual care group. At baseline, 20% of patients had diabetes mellitus, 81% had MI, 7% had CHF, and 8% had recent unstable angina.
Indirectness of population	No indirectness
Interventions	(n=800) Intervention 1: High intensity statin - Atorvastatin 20 mg. Atorvastatin 20 mg/day (for most participants). Starting dose was 10 mg/day. If the goal of LDL cholesterol of <100 mg/day was not reached within 6 weeks, the dose was increased to 20 mg/day. With evaluations every 6 weeks the dose was titrated up to 80 mg/day. The average dose was 24 mg/day (4% of patients had 10 mg/day, 82% 20 mg/day, 11% 40 mg/day, and 3% 80 mg/day). Duration mean 3 years. Concurrent medication/care: 89% patients were taking aspirin or other antiplatelet agents, 86% were taking beta blockers, 55% were taking ACE inhibitors or ATI antagonists, 13% were taking nitrates, 25% were taking calcium channel blockers, 11% were taking diuretics, and 98% were taking hypolipidemic drugs (n=800) Intervention 2: Placebo. Usual care - this included lifestyle changes, such as hypolipidemic diet, weight loss, excercise plus any neccessary drug treatment (for example, lipid-lowering agents). Duration mean 3 years. Concurrent medication/care: Simvastatin was used in 5% of usual care patients, atorvastatin in 3%, pravastatin in 3% and fluvastatin in 1%. 86% patients were taking aspirin or other antiplatelet agents, 84% were taking beta-blockers, 53% were taking ACE inhibitors or ATI antagonists, 16% were taking nitrates, 28% were taking calcium channel blockers, 13% were taking diuretics, and 14% were taking hypolipidemic drugs.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3 years; Group 1: 21/800, Group 2: 51/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 9/800, Group 2: 17/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total mortality at 3 years; Group 1: 23/800, Group 2: 40/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Coronary mortality at 3 years; Group 1: 20/800, Group 2: 38/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at 3 years; Group 1: 0/800, Group 2: 0/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : Liver enzyme increase > 3-fold of the upper limit of normal at 3 years; Group 1: 7/800, Group 2: 3/800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 2.51 mmol/l (SD 0.1); n=800, Group 2: mean 4.37 mmol/l (SD 0.83); n=800; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Baigent 2005[132]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=448)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with CKD: Adults with CKD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 or older, predialysis patient with the most recent serum or plasma creatinine level of 1.7 mg/dL or greater (≥150 micromol/litre), a haemodialysis or peritoneal dialysis patient or had a functioning renal transplant (with any creatinine level) and their own nephrologist or primary care physician did not consider there was a definite indication for or contraindication to cholesterol lowering therapy or aspirin.
Exclusion criteria	Physician considered that cholesterol-lowering therapy should be prescribed, recent history of acute uraemia, history of chronic liver disease, inflammatory muscle disease (for example, dermatomyositis or polymyositis) or creatinine kinase level >3 times ULN, previous adverse reaction to statin or history of aspirin hypersensitivity, concurrent treatment with a contraindicated drug (non-study statin, fibrate, niacin, macrolide antibiotic, systemic azole antifungal, nefazodone, oral anticoagulant therapy), high immediate risk for bleeding (active peptic ulceration, recent injury or haemophilia), child bearing potential with absence of a reliable method of contraception, a life-threatening condition other than CKD or vascular disease, frequent non-attendance or known non-compliance or drug/alcohol abuse.
Recruitment/selection of patients	Patients randomised between October 1999 and March 2001, recruitment was discontinued after an interim analysis showed that the annual rate of major bleeding events was less than anticipated.

Age, gender and ethnicity	Age - Mean (SD): Simvastatin only 52 (15) years, simvastatin plus aspirin 54 (14) years, aspirin only 52 (16) years, double Placebo 54 (15) years. Gender (M:F): Male/Female Ratio Simvastatin only 79/33 Simvastatin Aspirin 78/34 Aspirin only 81/32 Double Placebo 76/35. Ethnicity: Simvastatin Aspirin: White 92% Black 3.6% Indian 3.6% Other 0.9%. Simvastatin Only: White 88.4% Black 7.1% Indian 1.8% Other 1.8%. Aspirin Only: White 88.5% Black 7.1%, Indian 3.5%, Other 0.9%. Double Placebo: White 91% Black 5.4% Indian 3.6% Other 0%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	2x2 factorial design with simvastatin only, simvastatin plus aspirin, aspirin only and double placebo groups. Baseline characteristics: Diabetes; simvastatin plus aspirin 10.7%, simvastatin only 10.7%, aspirin only 11.5%, double placebo 9.9%. Baseline total cholesterol mmol/l: simvastatin 5.22, placebo 5.15, total cholesterol at 1 year mmol/l; simvastatin 4.22, placebo 5.07. Baseline LDL-cholesterol mmol/l; simvastatin 3.21, placebo 3.13, LDL-cholesterol at 1 year mmol/l simvastatin 2.3, placebo 2.95.
Indirectness of population	No indirectness
Interventions	(n=224) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: Not reported Comments: 42 (19%) stopped Simvastatin active treatment during the trial (n=224) Intervention 2: Placebo. N/A. Duration 1 year. Concurrent medication/care: Not reported Comments: 40 (18%) stopped placebo Simvastatin during the trial
Funding	Study funded by industry (Merck & Co.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years	

- Actual outcome for Adults with CKD: CK >10 times normal at 1 year; Group 1: 1/224, Group 2: 0/224; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with CKD: ALT >3 times normal level at 1 year; Group 1: 2/224, Group 2: 1/224; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Beishuizen 2004[158] (Beishuizen 2005[156])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Netherlands; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with type 2 diabetes: Type 2 diabetes without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with type 2 diabetes for at least 1 year, aged 30-80 years, without a history of CVD (defined as CAD, ECG criteria for a past MI, ischaemic stroke, peripheral artery bypass surgery, percutaneous transluminal angioplasty or amputation because of atherosclerotic disease), fasting total cholesterol 4.0-6.9 mmol/L, triglycerides <6.0 mmol/l.
Exclusion criteria	CK more than 3 times ULN, ALT more than 2 times ULN, creatinine clearance <30 ml/min, use of lipid lowering therapy within 8 weeks of start of the trial.
Recruitment/selection of patients	Patients were recruited from the departments of internal medicine at 2 non-academic teaching hospitals in the Netherlands.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 58.8 (11.3) years, placebo 58.2(11.4). Gender (M:F): Simvastatin 61/64, placebo 57/68. Ethnicity: Simvastatin Caucasian 66% Indo-Asian 22% other 11%. Placebo Caucasian 69% Indo-Asian 16% other 15%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Initially, patients were randomised to receive either cerivastatin or placebo. In August 2011, when cerivastatin was withdrawn from the market, participants were instructed to discontinue trial medication. The study was not unblinded and 1 month later cerivastatin was replaced by simvastatin. Statin and matching placebo were given according to original allocation. Baseline total cholesterol mean mmol/l; simvastatin 5.49, placebo 5.60, at 2 years simvastatin 4.49, placebo 5.74. Baseline LDL-cholesterol mean mmol/l; simvastatin 3.44, placebo 3.55, at 2 years simvastatin 2.58, placebo 3.78.
Indirectness of population	No indirectness
Interventions	(n=125) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day (Merck Sharp & Dohme). Duration 2 years. Concurrent medication/care: Insulin 50% (n=125) Intervention 2: Placebo. N/A. Duration 2 years. Concurrent medication/care: Insulin 55%
Funding	Equipment / drugs provided by industry (Bayer, Merck Sharp & Dohme)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with type 2 diabetes: Non-fatal coronary events at 2 years; Group 1: 0/125, Group 2: 4/125; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with type 2 diabetes: CK elevated at 2 years; Group 1: 0/125, Group 2: 0/125; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at 2 years; Group 1: 3/125, Group 2: 4/125; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Myalgia at 5 years

- Actual outcome for Adults with type 2 diabetes: Myalgia at 2 years; Group 1: 18/125, Group 2: 26/125; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with type 2 diabetes: ALT >3 times normal level at 2 years; Group 1: 1/125, Group 2: 0/125; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with type 2 diabetes: LDL-cholesterol at 2 years; Group 1: mean 2.64 mmol/l (SD 0.96); n=125, Group 2: mean 3.76 mmol/l (SD 0.83); n=125; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Byington 1995[256] (Furberg 1993,[526] Furberg 1994,[525] Crouse 1995[362])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=151)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Extracranial carotid atherosclerosis quantified by B-mode ultrasonography
Stratum	Adults with established CVD : Men and women with moderately elevated LDL cholesterol levels and CAD
Subgroup analysis within study	Stratified then randomised: Stratified by a patient's LDL-cholesterol concentration
Inclusion criteria	Coronary disease manifested by a history of heart attack (a documented acute MI with typical evolutionary ECG and enzyme changes) or by cardiac catheterisation with evidence of >50% stenosis; LDL-cholesterol levels had to be between the 60th and 90th percentiles for age and gender and diet-resistant. Patients also had to demonstrate at least 1 qualifying extracranial carotid lesion with an IMT≥1.3 mm on B-mode ultrasound examination.
Exclusion criteria	Plasma triglyceride concentration ≥350 mg/dL, secondary hyperlipidemia, recent myocardial infarction (≥6 months), severe or unstable angina pectoris, uncontrolled CHF or hypertension, significant gastrointestinal disease or surgery that might interfere with drug absorption, and treatment with certain drugs including corticosteroids, androgens, other lipid-lowering agents, or antacids containing aluminum salts.
Recruitment/selection of patients	The authors stated that 1700 participants were identified, but most were excluded due to lipid values outside of the eligibility criteria. Trial follow-up ended in January 1993 (no other details reported).
Age, gender and ethnicity	Age - Mean (SD): 63 years (SD not reported). Gender (M:F): 85%/15%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol (mg/dL): mean (SE) pravastatin; 235.6 (2.86) and 234.1 (2.33) placebo; LDL-cholesterol: mean (SE) pravastatin; 167.5 (2.24) and 164.3 (2.07) placebo; After 3 years: total cholesterol (mg/dl): mean (SE) pravastatin; 185.7 (2.49) and 235.0 (2.47) placebo; LDL-cholesterol: mean (SE) pravastatin; 120.3 (SE 2.20) and 166.6 (2.20) placebo; Baseline data on percentage of people with diabetes, and prior MI or stroke were not reported.
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 10-40 mg/day. Duration 3 years. Concurrent medication/care: Not reported Comments: 4% of patients had pravastatin 10 mg/day and 23.5% had 20 mg/day dosage (n=76) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: Not reported Comments: 4 patients in the placebo group were placed on active medication by their physicians during the 3 years of follow-up
Funding	Study funded by industry (Bristol-Myers Squibb to the Bowman Gray School of Medicine)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal plus fatal MI at 3 years; Group 1: 2/75, Group 2: 10/76; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Mortality at 3 years; Group 1: 3/75, Group 2: 5/76; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 3.11 mmol/l (SD 0.59); n=75, Group 2: mean 4.31 mmol/l (SD 0.56); n=76;

Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Cannon 2004**[265]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4162)
Countries and setting	Conducted in Australia, Canada, United Kingdom, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Hospitalised for an acute coronary syndrome within the preceding 10 days
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women who were at least 18 years old were eligible for inclusion if they had been hospitalised for ACS (acute MI (with or without ECG evidence of ST-segment elevation) or high-risk unstable angina in the preceding 10 days). Patients had to be in stable condition and were to be enrolled after a percutaneous revascularisation procedure if one was planned. Finally, patients had to have a total cholesterol level of 240 mg/dL (6.21 mmol/l) or less, measured at the local hospital within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours. Patients who were receiving long-term lipid-lowering therapy at the time of their index acute coronary syndrome had to have a total cholesterol level of 200 mg/dL (5.18 mmol/l) or less at the time of screening in the local hospital.
Exclusion criteria	Coexisting condition expected to shorten survival to less than 2 years, were receiving therapy with any statin at a dose of 80 mg/day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomisation, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomisation or were likely to require such treatment during the study period (because atorvastatin is metabolised by this pathway), had undergone PCI within the previous 6 months (other than for the qualifying event) or CABG within the previous 2 months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious

	hepatic disease, had an unexplained elevation in the creatine kinase level that was more than 3 times ULN and that was not related to MI, or had a creatinine level of more than 2.0 mg/dL (176.8 micromol/litre).
Recruitment/selection of patients	Between Nov 2000 and Dec 2001.
Age, gender and ethnicity	Age - Mean (SD): 58 years. Gender (M:F): 78%/22%. Ethnicity: White 91%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Lipid values (mmol/l). Baseline: Total cholesterol: 4.65 (pravastatin 40 mg), 4.68 (atorvastatin 80 mg); LDL-cholesterol: 2.74 (pravastatin 40 mg), 2.74 (atorvastatin 80 mg). End of study: LDL-cholesterol: 2.46 (pravastatin), 1.60 (atorvastatin 80 mg). Prior MI: 18%; CABG: 11%; diabetes mellitus: 18%.
Indirectness of population	No indirectness
Interventions	(n=2063) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 2 years. Concurrent medication/care: Dietary counselling: 100% of patients, aspirin: 93%, warfarin: 8%, clopidogrel or ticlodipine: 72% percent initially and 20% at 1 year, beta-blockers: 85%, ACE inhibitors: 69%, ARBs: 14% (n=2099) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Dietary counselling: 100% of patients, aspirin: 93%, warfarin: 8%, clopidogrel or ticlodipine: 72% percent initially and 20% at 1 year, beta blockers: 85%, ACE inhibitors: 69%, ARBs: 14%
Funding	Study funded by industry (Bristol-Myers Squibb and Sankyo)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : MI at 2 years; Group 1: 153/2063, Group 2: 139/2099; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years - Actual outcome for Adults with established CVD : Stroke at 2 years; Group 1: 21/2063, Group 2: 21/2099; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 2 years; Group 1: 0/2063, Group 2: 0/2099; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 2 years; Group 1: 66/2063, Group 2: 46/2099; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death from CHD at 2 years; Group 1: 29/2063, Group 2: 23/2099; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Elevation in alanine aminotransferase>3 times upper limit of normal at 2 years; Group 1: 23/2063, Group 2: 69/2099; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Colhoun 2004[330] (Colhoun 2005,[332] Armani 2006,[106] Hitman 2007,[655] Newman 2008,[1019] Charlton-Menys 2009,[298] Colhoun 2009[331])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2841)
Countries and setting	Conducted in Irish Republic, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diabetes mellitus defined using the 1985 WHO criteria
Stratum	Adults with type 2 diabetes: Patients with type 2 diabetes without high concentrations of LDL-cholesterol
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analyses were conducted by age, sex, and baseline lipids. In addition, post hoc subgroup analysis was conducted in patients without a prior history of cardiovascular disease (Colhoun 2005), by kidney status (Colhoun 2009), and baseline ratios of ApoB and ApoA-I (Charlton-Menys et al. 2009)
Inclusion criteria	Men and women aged 40-75 years with type 2 diabetes mellitus diagnosed at least 6 months before study entry were included as long as they had at least 1 or more of the following: a history of hypertension; retinopathy; microalbuminuria or macroalbimnuria; or currently smoking. All patients reported current smoking were counselled to quit. Mean serum LDL-cholesterol had to be 4.14 mmol/l or lower and serum triglycerides 6.78 mmol/l or less during baseline visits.
Exclusion criteria	Past history of MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease, plasma creatinine concentration >150 micromol/litre, glycated haemoglobin of more than 12%, or if during the baseline phase they had less than 80% compliance with placebo.
Recruitment/selection of patients	Investigators identified potentially eligible individuals by reviewing computerised registers of patients and by opportunistic assessment of people attending diabetes clinics. Patients were randomised between Nov 1997 and June 2001.

Age, gender and ethnicity	Age - --: . Gender (M:F): 68%/32%. Ethnicity: 95% White
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Lipid values mean (SD) (mmol/l) - Baseline total cholesterol; 5.36 (0.83) in atorvastatin group and 5.35 (0.82) in the placebo group, LDL-cholesterol; 3.04 (0.72) in atorvastatin group and 3.02 (0.70) in the placebo group. At 4 years total cholesterol; 4.12 (0.84) in atorvastatin group and 5.28 (0.91) in the placebo group, LDL-cholesterol (mmol/); 2.11 (0.70) in atorvastatin group and 3.12 (0.80) in the placebo group. There was no information on the percentage of people with cerebrovascular disease at baseline (as this was part of the exclusion criteria). All patients had diabetes.
Indirectness of population	No indirectness
Interventions	(n=1429) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 3.9 years. Concurrent medication/care: If lipid-lowering had to be started for any clinical indication during the study period the investigator could prescribe additional treatment on top of study drug including: atorvastatin 10 mg; simvastatin (up to) 40 mg, pravastatin (up to) 40 mg; fluvastatin (up to) 80 mg, and cerivastatin 0.3 mg (before its withdrawal). (n=1412) Intervention 2: Placebo. Placebo. Duration Median 3.9 years. Concurrent medication/care: If lipid-lowering had to be started for any clinical indication during the study period the investigator could prescribe additional treatment on top of study drug including: atorvastatin 10 mg; simvastatin (up to) 40 mg, pravastatin (up to) 40 mg; fluvastatin (up to) 80 mg, and cerivastatin 0.3 mg (before its withdrawal).
Funding	Study funded by industry (The study was funded by Diabetes UK, the UK Department of Health, Pfizer UK, and Pfizer Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO Protocol outcome 1: Non-fatal MI at 5 years	

- Actual outcome for Adults with type 2 diabetes: Non-fatal MI at Median 3.9 years; Group 1: 25/1428, Group 2: 41/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with type 2 diabetes: Non-fatal stroke at Median 3.9 years; Group 1: 39/1428, Group 2: 21/1410; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Non-fatal stroke at Median 3.9 years; HR 0.52 (95%CI 0.31 to 0.89) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with type 2 diabetes: Rhabdomyolysis at Median 3.9 years; Group 1: 0/1428, Group 2: 0/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 3.9 years; Group 1: 61/1428, Group 2: 82/1410; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 3.9 years; HR 0.73 (95%CI 0.52 to 1.01) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with type 2 diabetes: Fatal MI and other acute coronary heart disease death at Median 3.9 years; Group 1: 18/1428, Group 2: 24/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with type 2 diabetes: Myalgia (treatment associated) at Median 3.9 years; Group 1: 14/1428, Group 2: 17/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with type 2 diabetes: Alanine transaminase and aspartate transaminase >3 times the upper limit of normal at Median 3.9 years; Group 1: 23/1428, Group 2: 18/1410; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with type 2 diabetes: LDL-cholesterol reduction at Median 3.9 years; Group 1: mean 2.11 mmol/l (SD 0.71); n=1429, Group 2: mean 3.12 mmol/l (SD 0.8); n=1412; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Crouse 2007[365]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=876)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : low risk for CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 45 to 70 years (men) or 45 to 70 years (women); screening LDL-cholesterol level of 120 to less than 190mg/dL (3.1 to <4.9mmol/l) for those with only age as CHD risk factor or 120 to less than 160mg/dL (3.1 to <4.1 mmol/l) for individuals with 2 or more CHD risk factors and a 10 year risk of CHD events of less than 10%; HDL-cholesterol level of 60 mg/dL or lower (≤1.6mmol/l); level of triglycerides lower than 500mg/dL (<5.7 mmol/l); and maximum CIMT measurements between 1.2 mm and less than 3.5 mm from 2 separate ultrasound examinations.
Exclusion criteria	Use of lipid lowering therapies in the previous 12 months, clinical evidence of CAD or other peripheral atherosclerotic disease, prior revascularisation procedures, 10 year CHD risk 10% or more, diabetes mellitus, uncontrolled hypertension, or familial hypercholesterolaemia, or serum creatinine concentration higher than 2mg/dL (>177 micromol/litre).
Recruitment/selection of patients	Study conducted at 61 primary care centres in the USA and Europe between Aug 2002 and May 2006.
Age, gender and ethnicity	Age - Mean (SD): Rosuvastatin 57 (6.2) years, placebo 57 (6.0) years. Gender (M:F): Rosuvastatin 421/281; Placebo 167/115. Ethnicity: White race(%) Rosuvastatin 94 Placebo 95

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Total cholesterol baseline mean (mmol/l); rosuvastatin 5.92, placebo 5.95, total cholesterol at 2 years; rosuvastatin 3.93, placebo 5.97. LDL-cholesterol at baseline mean (mmol/l); rosuvastatin 4.01, placebo 3.98, LDL-cholesterol at 2 years; rosuvastatin 2.07, placebo 3.98.
Indirectness of population	No indirectness
Interventions	(n=282) Intervention 1: Placebo. N/A. Duration 2 years. Concurrent medication/care: Aspirin 3%, Antihypertensive 14% (n=702) Intervention 2: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg. Duration 2 years. Concurrent medication/care: Aspirin 2%, Antihypertensive 14%
Funding	Study funded by industry (AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Adverse event report of myocardial infarction at 2 years; Group 1: 1/700, Group 2: 0/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis at 2 years; Group 1: 1/700, Group 2: 2/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Adverse event report of all deaths at 2 years; Group 1: 1/700, Group 2: 0/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Myalgia at 5 years - Actual outcome for Adults without established CVD : Myalgia at 2 years; Group 1: 89/700, Group 2: 34/281; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults without established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 2 years; Group 1: 4/700, Group 2: 1/281; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**De lemos 2004[398]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4497)
Countries and setting	Conducted in Argentina, Australia, Belgium, Chile, China, Colombia, Croatia, Estonia, Finland, France, Germany, Greece, Hong Kong (China), Hungary, Israel, Italy, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, USA, Venezuela; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Up to 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with ACS
Subgroup analysis within study	Not applicable
Inclusion criteria	Phase A. Open-label noninferiority trial comparing enoxaparin with unfractionated heparin in patients with non–ST-elevation ACS who were treated with tirofiban and aspirin. Patients were required to have chest pain at rest lasting 10 minutes or longer within the previous 24 hours, which was associated with either ST elevation or depression of 0.5 mm or higher, or with elevated levels of creatine kinase–MB or troponin. Phase Z. Patients between the ages of 21 and 80 years with either non–ST-elevation ACS or ST-elevation MI; total cholesterol level ≤6.48 mmol/l. Initially, patients were entered into phase Z only if they presented with non–ST-elevation ACS, were stabilised during phase A of the trial for at least 12 consecutive hours within 5 days after symptom onset, and met at least 1 of the following high-risk characteristics: age older than 70 years; diabetes mellitus; prior history of CAD, PAD, or stroke; elevation of serum creatine kinase–MB or troponin levels; recurrent angina with ST-segment changes; ECG evidence of ischemia on a predischarge stress test; or multivessel coronary artery disease determined by coronary angiography. Patients enrolled in phase A who did not meet stability and high-risk criteria were not eligible for continuation to phase Z. The protocol was amended to allow patients with non–ST-elevation ACS who were not enrolled in phase A and patients with ST-elevation MI to enter directly into phase Z. Patients in the latter category were required to receive fibrinolytic therapy

	or PCI if they presented within 12 hours of symptom onset and no reperfusion therapy if symptom onset was longer than 12 hours prior to presentation. Patients were also required to meet criteria for stability and have at least 1 high-risk feature in addition to cardiac biomarker elevation.
Exclusion criteria	Patients receiving statin therapy at the time of randomisation, if CABG was planned, or if PCI was planned within the first 2 weeks after enrollment. Patients with alanine aminotransferase (ALT) level >20% above ULN; increased risk for myopathy due to renal impairment (serum creatinine level >2.0 mg/dl [176.8 micromol/litre]) or concomitant therapy with agents known to enhance myopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; prior history of nonexercise-related elevations in creatine kinase level or nontraumatic rhabdomyolysis.
Recruitment/selection of patients	Phase Z of the A to Z trial.
Age, gender and ethnicity	Age - Median (range): 61 (52-69). Gender (M:F): 76%/24%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear
Extra comments	. Lipid levels in mmol/l. Baseline (simvastatin 20 mg): Total cholesterol: 4.77 (4.27-5.34); LDL-cholesterol: 2.87 (2.46-3.39). Baseline (simvastatin 80 mg): Total cholesterol: 4.79 (4.22-5.31); LDL-cholesterol: 2.90 (2.43-3.37). 2-years (simvastatin 20): Total-cholesterol: 4.07 (3.57-4.56); LDL-cholesterol: 2.10 (1.71-2.49). 2-years (simvastatin 80 mg): Total cholesterol: 3.57 (3.16-4.09); LDL-cholesterol: 1.71 (1.40-2.12). Values expresses as median (25th-75th percentiles) mmol/l. Diabetes: 24%. Hypertension: 50%. STEMI: 40%. Non-ST-segment elevation ACS: 60%.
Indirectness of population	No indirectness
Interventions	(n=2232) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Placebo for 4 months followed by simvastatin 20 mg/day. Duration 2 years. Concurrent medication/care: Aspirin: 98%; beta blockers: 90%; ACE inhibitors: 72% Comments: Patients who had LDL-cholesterol levels >3.37 mmol/l at month 8 or any subsequent visit were provided additional dietary, lifestyle, and compliance counseling. If after 6 weeks the LDL-cholesterol level remained >3.37 mmol/l, the investigator could either add a bile acid sequestrant or discontinue the study drug and initiate open-label statin therapy. The study drug was discontinued if the LDL-cholesterol level was 1.04 mmol/l or lower.

	(n=2265) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 40 mg/day for 1 month followed by simvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Aspirin: 98%; beta blockers: 90%; ACE inhibitors: 70% Comments: Patients who had LDL-cholesterol levels >3.37 mmol/l at month 8 or any subsequent visit were provided additional dietary, lifestyle, and compliance counseling. If after 6 weeks the LDL-cholesterol level remained >3.37 mmol/l, the investigator could either add a bile acid sequestrant or discontinue the study drug and initiate open-label statin therapy. The study drug was discontinued if the LDL-cholesterol level was 1.04 mmol/l or lower.
Funding	Study funded by industry (Merck & company, Whitehouse Station, NJ)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 2 years; HR 0.79 (95%CI 0.61 to 1.02) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : CV mortality at 2 years; HR 0.75 (95%CI 0.57 to 1) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : MI at 2 years; Group 1: 155/2232, Group 2: 151/2265; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : MI at 2 years; HR 0.96 (95%CI 0.77 to 1.21) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 2 years; Group 1: 35/2232, Group 2: 28/2265; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Stroke at 2 years; HR 0.79 (95%CI 0.48 to 1.3) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Levels of CK >10 times the upper limit of normal at 2 years; Group 1: 1/2230, Group 2: 9/2263; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: All-cause mortality at 5 years

- Actual outcome for Adults with established CVD : All-cause mortality at 2 years; Group 1: 130/2232, Group 2: 104/2265; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 2 years; Group 1: 109/2232, Group 2: 83/2265; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 8: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Levels of AST or ALT >3 times the upper limit of normal at 2 years; Group 1: 8/2068, Group 2: 19/2132; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Deedwania 2007[412]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=893)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : History of CAD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 65-85 years; documented history of CAD; baseline LDL-cholesterol between 2.6-6.5 mmol/l; ≥1 episode of myocardial ischemia with a total duration of ≥3 minutes during 48-hour ambulatory ECG monitoring at the screening visit.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients already receiving lipid-lowering therapy entered a washout period of ≥6 weeks; patients on digitalis glycosides underwent a 4-week washout period.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin: 72.4 (5.1) years, pravastatin: 72.6 (5.2) years. Gender (M:F): 70%/30%. Ethnicity: White (97%)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men

	and women).
Extra comments	. Baseline values (mmol/l). Total cholesterol: atorvastatin 5.8, pravastatin 5.7. LDL-cholesterol: atorvastatin 3.8, pravastatin 3.7. Least-squares mean percent changes in lipid parameters at 1 year: Total cholesterol: atorvastatin -39.5, pravastatin -21.3. LDL-cholesterol: atorvastatin -55.4, pravastatin -32.4. MI: atorvastatin 45.5%, pravastatin 46.3%. Cerebrovascular accident: atorvastatin 2.2%, pravastatin 6.1%. CABG: atorvastatin 26.5%, pravastatin 32.4%. Angioplasty: atorvastatin 31.6%, pravastatin 28.5%. Angina: atorvastatin 94.4%, pravastatin 93.0%. Hypertension: atorvastatin 66.4%, pravastatin 62.7%. CHF: atorvastatin 5.4%, pravastatin 5.2%. Diabetes mellitus: atorvastatin 22.4%, pravastatin 24.0%.
Indirectness of population	No indirectness
Interventions	(n=445) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 1 year. Concurrent medication/care: Not stated (n=446) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 1 year. Concurrent medication/care: Not stated
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 1 year; Group 1: 3/445, Group 2: 1/446; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 1 year; Group 1: 0/445, Group 2: 0/446; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : CPK >10 times ULN at 1 year; Group 1: 1/445, Group 2: 0/446; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 1 year; Group 1: 18/445, Group 2: 6/446; Risk of bias: Low; Indirectness of outcome: No

indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 1 year; HR 0.31 (95%CI 0.12 to 0.79) Calculated – from Kaplan Meier curve; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 1 year; Group 1: 10/445, Group 2: 4/445; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event: Myalgia at 5 years - Actual outcome for Adults with established CVD : Myalgia at 1 year; Group 1: 5/445, Group 2: 8/446; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : ALT or AST >3 times ULN at 1 year; Group 1: 1/445, Group 2: 19/446; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Egede 2013[454]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=87)
Countries and setting	Conducted in Denmark; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic assessment
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	1) STEMI; 2) No prior treatment with statins or other lipid lowering drugs; and 3) a non-significant lesion in 1 of the 2 non-culprit coronary arteries (angiographic diameter stenosis ≥20% and <50%.
Exclusion criteria	1) age below 18 or above 81 years; 2) unconscious patients; 3) serum creatinine >176 micromol/litre; 4) hypothyroidism (TSH >1.5 times ULN); 5) current liver disease (ALAT >2 times ULN); 6) unexplained creatine kinase; 8) prior myopathy or serious hypersensitivity reaction caused by statins; 9) women with child-bearing potential not using chemical or mechanical contraception; 10) pregnant or breastfeeding women; 11) history of malignancy unless a disease-free period of more than 5 years was present; 12) participation in another RCT; 13) treatment with cyclosporine or fibrates.
Age, gender and ethnicity	Age - Mean (SD): Low dose rosuvastatin 60.0 (10.3) years, high dose rosuvastatin 62.0 (9.9) years. Gender (M:F): 73:14. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men

	and women).
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: High intensity statin - Rosuvastatin 10 mg. Rosuvastatin 5 mg/day. Duration 1 year. Concurrent medication/care: Beta blockers, calcium antagonists, ACE inhibitors, ATII inhibitors, diuretics (n=43) Intervention 2: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg/day. Duration 1 year. Concurrent medication/care: Beta blockers, calcium antagonists, ACE inhibitors, ATII inhibitors, diuretics
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 10 MG versus ROSUVASTATIN 40 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 1.6 mmol/l (SD 0.7); n=39, Group 2: mean 1.6 mmol/l (SD 0.7); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Gottlieb 2008[574]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=31)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic confirmation.
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years, required to have documented atherosclerosis in at least 1 vascular territory defined as: at least moderate (>3.9 mm wall thickness) aortic atherosclerosis seen on transoesophageal echocardiography or moderate coronary heart disease (>50% stenosis) in at least 1 coronary artery seen at cardiac catheterisation or more than 50% carotid lesion or symptomatic peripheral vascular disease as assessed by ultrasound. Not on a dose equivalent to or greater than 80 mg of simvastatin.
Exclusion criteria	Metallic implants and claustrophobia, contraindications for a nasogastric catheterisation, elevated baseline liver transaminases and serum creatinine (>2 times normal) or inability to give informed consent.
Recruitment/selection of patients	Single centre
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 80 mg; 71.3 (8.3) years, simvastatin 20 mg; 65.5 (9.3) years. Gender (M:F): 24:7. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: Not reported (n=19) Intervention 2: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg/day. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Merck, National Institute Aging, Donald W Reynolds Johns Hopkins CV Center, NIH/NCRR grant, NHLBI grant, Johns Hopkins Field Center)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus SIMVASTATIN 80 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.63 mmol/l (SD 0.19); n=12, Group 2: mean 1.6 mmol/l (SD 0.7); n=19; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Hong 2008[669]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in South Korea; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Quantitative coronary angiography
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Angina patients who had mild to moderate degree of coronary stenosis with vulnerable plaque. A mild to moderate degree of coronary stenosis was defined as a diameter stenosis of 30% to 60%. Vulnerable plaque was defined as plaque with a large lipid core with a thin fibrous cap.
Exclusion criteria	MI, severe LVDF (ejection fraction <40%), hepatic or renal dysfunction.
Recruitment/selection of patients	Recruited from hospital.
Age, gender and ethnicity	Age - Mean (SD): Rosuvastatin 60 (8) years, atorvastatin 62 (9) years. Gender (M:F): 18/12. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: (Men and women).

Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: High intensity statin - Rosuvastatin 20 mg. Rosuvastatin. Duration 1 year. Concurrent medication/care: Aspirin, clopidigrel, ACE inhibitor, ARB, beta blocker, calcium channel blocker (n=14) Intervention 2: High intensity statin - Atorvastatin 40 mg. Atorvastatin. Duration 1 year. Concurrent medication/care: Aspirin, clopidigrel, ACE inhibitor, ARB, beta blocker, calcium channel blocker
Funding	Academic or government funding (The Korean Society of Circulation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 20 MG versus ATORVASTATIN 40 MG Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 12 months; Group 1: 0/16, Group 2: 0/14; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at baseline and follow-up, mean change at 12 months; Group 1: mean 1.68 mmol/l (SD 0.64); n=16, Group 2: mean 1.86 mmol/l (SD 0.67); n=14; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Hong 2009[668]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in South Korea; Setting: Cardiovascular Centre
Line of therapy	1st line
Duration of study	Intervention time: I year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Adults with CV disease
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients with de novo nonculprit/nontarget lesions without significant stenosis by coronary angiogram (diameter stenosis <50%), lesions with a plaque burden <0.75 by gray-scale IVUS, and lesions located in 1 of 3 major epicardial arteries in which stent implantation was not performed.
Exclusion criteria	Patients with severly calcific lesions, haemodynamically unstable patients, cardiogenic shock, recommended CABG, and previous history of administration of lipid-lowering agents including statin.
Recruitment/selection of patients	Not specified.
Age, gender and ethnicity	Age - Mean (SD): 50 years (SD not reported). Gender (M:F): 77%/23%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) (mg/dL): 191 (34) in simvastatin group and 189 (27) in the rosuvastatin group; LDL-cholesterol mean SD) (mg/dL): 119 (30) in simvastatin group and 116 (28) in the rosuvastatin group. There was no information on the percentage of people with cerebrovascular disease at baseline (as this was part of the exclusion criteria), 26% had diabetes in the simvastatin group and 22% had diabetes in the rosuvastatin group.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20mg/day. Duration 1 year. Concurrent medication/care: At baseline: nitrates: 92%; calcium channel blocker: 82%; beta blocker: 80%; angiotensin II receptor antagonist: 28%; angiotensin-converting enzyme inhibitor: 22% (n=50) Intervention 2: High intensity statin - Rosuvastatin 10 mg. Rosuvastatin 10 mg/day. Duration 1 year. Concurrent medication/care: At baseline: nitrates: 94%; calcium channel blocker: 86%; beta blocker: 76%; angiotensin II receptor antagonist: 24%; angiotensin-converting enzyme inhibitor: 20%
Funding	Academic or government funding (Partly supported by Cardiovascular Research Foundation, Seoul, Korea and a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus ROSUVASTATIN 10 MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Death due to any cause at 1 year; Group 1: 0/50, Group 2: 0/50; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.01 mg/dl (SD 0.52); n=50, Group 2: mean 1.66 mg/dl (SD 0.54); n=50; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years;

	Quality of life at 5 years

Study	**Ito 2001**[702]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=665)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3.9 years (median)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥60 years; serum total cholesterol levels 5.7-7.2 mmol/l.
Exclusion criteria	Familial and secondary hypercholesterolemia.
Recruitment/selection of patients	Recruited from 52 hospitals, universities and clinics across Japan.
Age, gender and ethnicity	Age - Mean (SD): 72.8 (5.7). Gender (M:F): 138/527. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline values mean (mmol/l): Total cholesterol: Pravastatin 5 mg: 6.5; Pravastatin 20 mg: 6.5. LDL-cholesterol: Pravastatin 5 mg: 4.2; Pravastatin 20 mg: 4.3. MI: Pravastatin 5 mg: 3%; Pravastatin 20 mg: 3%. Angina pectoris:

	Pravastatin 5 mg: 10%; Pravastatin 20 mg: 9%. CVD: Pravastatin 5 mg: 14%; Pravastatin 20 mg: 11%. ASO: MI: Pravastatin 5 mg: 1%; Pravastatin 20 mg: 1%. Diabetes mellitus: Pravastatin 5 mg: 31%; Pravastatin 20 mg: 29%. Hypertension: Pravastatin 5 mg: 51%; Pravastatin 20 mg: 50%. Decrease in cholesterol levels from baseline between 3 months and 3 years: Total cholesterol: Pravastatin 5 mg: 11-13%; Pravastatin 20 mg: 15-17%; LDL-cholesterol: Pravastatin 5 mg: 17-20%; Pravastatin 20 mg: 23-26%.
Indirectness of population	No indirectness
Interventions	(n=334) Intervention 1: Low intensity statin - Pravastatin 5 mg. Pravastatin 5 mg/day. Duration 3.9 years. Concurrent medication/care: Not reported (n=331) Intervention 2: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day. Duration 3.9 years. Concurrent medication/care: Not reported
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 5 MG versus PRAVASTATIN 20 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome: Non-fatal MI at 3.9 years; Group 1: 4/334, Group 2: 1/331; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome: All-cause mortality at 3.9 years; Group 1: 20/334, Group 2: 14/331; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years
- Actual outcome: CV mortality at 3.9 years; Group 1: 6/334, Group 2: 8/331; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Knopp 2006[771]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2411)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Type 2 diabetes defined by WHO
Stratum	Adults with type 2 diabetes: Individuals with type 2 diabetes, with and without prior MI or interventional procedure, and LDL-cholesterol levels below guideline targets
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis was conducted in primary and secondary prevention diabetic subjects
Inclusion criteria	Males and females, aged 40-75 years, with type 2 diabetes diagnosed ≥3 years before screening, LDL-cholesterol ≥140 mg/dL if subjects had documented MI or an interventional procedure >3 months before screening or LDL cholesterol ≥160 mg/dL if not. Triglyceride levels were required to be ≥600 mg/dL at all visits. The protocol was amended 2 years after start of study to enroll subjects without prior MI or interventional procedure.
Exclusion criteria	Type I diabetes; MI, interventional procedure, or episodes of unstable angina ≥3 months before screening; HbA1c >10%; active liver disease or hepatic dysfunction; severe renal dysfunction or nephrotic syndrome; congestive heart failure treated with digoxin; creatine phosphokinase ≥3 times ULN; blood pressure >160/100 mmHg; BMI >35 kg/m2; abuse of alcohol and/or drugs; hypersensitivity to the study medication; participation in another clinical study within 30 days of screening; placebo run-in compliance rate <80%; current or planned pregnancy; or use of excluded medications (immunosuppressive agents, drugs know to interact with the study medications or affect clinical laboratory parameters, and drugs associated with increased risk of rhabdomyolysis with statins).
Recruitment/selection of patients	Recruited between 1996 and 1999 at 70 centres. Within 4 weeks of screening, subjects entered the 6-week, single-

	blind, placebo-baseline period, at the end of which baseline values were obtained and subjects were randomly assigned.
Age, gender and ethnicity	Age - Mean (SD): 61.1 (SD 8.1) years (atorvastatin) and 61.0 (SD 8.2) years (placebo). Gender (M:F): 66%/34%. Ethnicity: 84% white, 7% black
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (SD) (mg/dL): 194 (31) in both treatment groups: LDL-cholesterol mean (SD): 113 (25) in atorvastatin group and 114 (26) in placebo group. End of treatment: total cholesterol mean (mg/dL): -19.70 in atorvastatin group and -1.41 in placebo group; LDL-cholesterol: -30.29 in atorvastatin group and -1.09 in placebo group. At baseline, all people had diabetes, 16% people had had a prior MI, 13% had an interventional procedure, 16% had angina, 9% had PAD, 5% had cerebrovascular disease, and 9% had arrythmia.
Indirectness of population	No indirectness
Interventions	(n=1211) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 4 years. Concurrent medication/care: Concomitant medications: described as metabolic and nutritional: 98.3%, cardiovascular 78.7%, musculoskeletal: 71.9%, anti-infective: 57.1%, antihypertensive: 55.5%, and central nervous system: 53.9% (n=1199) Intervention 2: Placebo. Placebo. Duration Median 4 years. Concurrent medication/care: Concomitant medications: described as metabolic and nutritional: 98.1%, cardiovascular 84.4%, musculoskeletal: 71.8%, anti-infective: 55.8%, antihypertensive: 59.5%, and central nervous system: 52.6%
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO	

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with type 2 diabetes: Rhabdomyolysis at Median 4 years; Group 1: 1/1211, Group 2: 1/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 5 years - Actual outcome for Adults with type 2 diabetes: All-cause mortality at Median 4 years; Group 1: 70/1211, Group 2: 68/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults with type 2 diabetes: CV mortality at Median 4 years; Group 1: 38/1211, Group 2: 37/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: Adverse event: Myalgia at 5 years - Actual outcome for Adults with type 2 diabetes: Myalgia at Median 4 years; Group 1: 36/1211, Group 2: 19/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with type 2 diabetes: Abnormal liver function tests (no other details) at Median 4 years; Group 1: 17/1211, Group 2: 14/1199; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Koren 2004[785] (Koren 2005,[786] Koren 2009[784])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2442)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 51.5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CHD defined as a history of acute MI >3 months before screening, PCI > 6 months before screening, CABG >3 months before screening, or unstable angina > 3 months before screening.
Stratum	Adults with established CVD : Men and women with known CHD
Subgroup analysis within study	Unclear: Subgroup analyses (unclear if a priori or post hoc) were conducted by gender, age (Koren 2009), and race
Inclusion criteria	Men or women >18 years of age with known CHD; LDL-cholesterol levels between 110 mg/dL and 200 mg/dL for patients receiving lipid-lowering medication and between 130 mg/dL and 250 mg/dL for patients receiving no lipid-regulating therapy.
Exclusion criteria	None reported.
Recruitment/selection of patients	Patients were randomised between July 1995 and June 1998. The study was conducted in 16 centres (centres could be a staff model health maintenance organisation, a community physician open-provider health maintenance organisation, or a Veterans Affairs system). Letters were sent to patients inviting them to be screened for the study at research centres.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 61.1 (9.0) years, placebo 61.3 (8.6) years. Gender (M:F): 82%/18%. Ethnicity: 84% White/Caucasian; 11% Black; 0.8% Asian, 4% Other
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (SE) (mg/dl): mean 226 (1.0) in atorvastatin group and 225 (1.2) in placebo group; LDL-cholesterol mean (SE): mean 147 (0.8) in the atorvastatin group and 146 (0.9) in the placebo group. End of treatment: total cholesterol mean (SE) (mg/dl): mean 170 (1.1) in atorvastatin group and 189 (1.4) in placebo group; LDL-cholesterol mean (SE): mean 95 (0.8) in the atorvastatin group and 110 (0.8) in the placebo group. At baseline, 22% had diabetes, 58% had a prior MI, 39% had a PCI, 50% had CABG 21% had unstable angina, 7% had CHF, 7% had stroke, and 4% had peripheral revascularisation.
Indirectness of population	No indirectness
Interventions	(n=1217) Intervention 1: High intensity statin - Atorvastatin 80 mg. Patients were started on atorvastatin 10 mg/day which was doubled every 4 weeks until LDL-cholesterol level of <80 mg/dL or a max dose of 80 mg/day was achieved. The median dose of atorvastatin received by the patients was 40.5 mg/day (45% received 80 mg/day). Duration mean 51.5 months. Concurrent medication/care: Not reported (n=1225) Intervention 2: Placebo. Usual care: patients in the usual care group were maintained on the lipid-lowering programme already prescribed by their regular physicians (treated at the discretion of their physician). Duration Mean 51.5 months. Concurrent medication/care: Lipid regulating therapy could include atorvastatin after its approval in 1997
Funding	Study funded by industry (Parke-Davis and Pfizer Pharmaceuticals funded the study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at Mean 51.5 months; Group 1: 52/1217, Group 2: 94/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal MI at Mean 51.5 months; HR 0.52 (95%CI 0.38 to 0.74) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years - Actual outcome for Adults with established CVD : Stroke at Mean 51.5 months; Group 1: 35/1217, Group 2: 39/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Stroke at Mean 51.5 months; HR 0.87 (95%CI 0.55 to 1.38) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at Mean 51.5 months; Group 1: 0/1217, Group 2: 0/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at Mean 51.5 months; Group 1: 121/1217, Group 2: 127/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at Mean 51.5 months; HR 0.92 (95%CI 0.72 to 1.18) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Cardiac death at Mean 51.5 months; Group 1: 43/1217, Group 2: 61/1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Cardiac death at Mean 51.5 months; HR 0.69 (95%CI 0.47 to 1.02) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at Mean 51.5 months; Group 1: mean 2.46 mmol/l (SD 0.7); n=1217, Group 2: mean 2.84 mmol/l (SD 0.7); n=1225; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Larosa 2005[811] (Waters 2004,[141] Shepherd 2008[1250])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=10001)
Countries and setting	Conducted in Australia, France, Germany, Netherlands, United Kingdom, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: median of 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Patients with stable CHD
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged bewteen 35-75 years; clinical evident CHD defined by 1 or more; previous MI, angina with objective evidence of atherosclerotic CHD and a history of coronary revascularisation.
Exclusion criteria	Hypersensitivity to statin; liver disease or hepatic dysfunction defined as alanine or aspartate aminotransferase >1.5 times ULN; pregnant women or breastfeeding; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled Hypothyroidism; uncontrolled hypertension; a MI, coronary revascularisation procedure or severe/unstable angina within 1 month of screening; any planned surgical procedure for the treatment of atherosclerosis; an ejection fraction <30%; haemodynamically important valvular disease; gastrointestinal disease limiting drug absorption or partial ileal bypass; any nonskin malignancy, malignant melanoma or other survival-limiting disease; unexplained creatine phosphokinase levels >6 times ULN; concurrent therapy with long-term immunosuppressant; concurrent therapy with lipids-regulating drugs not specified as study treatment in the protocol; history of alcohol abuse; participation in another clinical trial concurrently or within 30 days before screening.
Recruitment/selection of patients	Any previously prescribed lipid-regulating drugs discontinued at screening, and patients require a wash-out period of ≥6 weeks before visit 2. After discontinuation, all eligible patients commence treatment with atorvastatin 10 mg/day on an open-label basis. Patients with LDL-cholesterol between 3.5-6.5 mmol/l and triglycerides ≤6.8 mmol/l at visit 2 are

	eligible to continue the study during the run-in period. Randomisation from July 1998 to December 1999. History of systemic hypertension: 53.7%; Diabetes mellitus: 15.0%; peripheral vascular disease: 11.0%; CHF: 7.6%.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 10 mg; 60.9 (8.8) years, atorvastatin 80 mg; 61.2 (8.8) years. Gender (M:F): 8099/1902. Ethnicity: white 94.1%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline values mean (SD) (mmol/l): Total cholesterol: 4.5 (0.7); LDL-cholesterol: 2.5± (0.5). 41.8% prior MI; 24.1% angina with evidence of coronary disease; 82.2% prior coronary revascularisation. 3107 patients had CKD at baseline (3070 had stage 3 CKD, eGFR 30-59 ml/min/1.73m2; 29 had stage 4 CKD, eGFR 15-29 ml/min/1.73m2).
Indirectness of population	No indirectness
Interventions	(n=4995) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atrovastatin 80 mg per day. Duration 4.9 years. Concurrent medication/care: Aspirin: 87.6%; beta blockers: 55.1%; calcium antagonist: 25.6%; ACE inhibitor: 27.6%; nitrates: 31.8%; current HRT: 3.05% of women; spironolactone: 22.4%; ARBs: 1.8% (n=5006) Intervention 2: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10mg per day. Duration 4.9 years. Concurrent medication/care: Aspirin: 87.6%; beta blockers: 55.1%; calcium antagonist: 25.6%; ACE inhibitor: 27.6%; nitrates: 31.8%; current HRT: 3.05% of women; spironolactone: 22.4%; ARBs: 1.8
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus ATROVASTATIN 80MG

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : death from any cause at 4.9years; HR 1.01 (95%CI 0.85 to 1.19) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : death from CHD at 4.9years; HR 0.8 (95%CI 0.61 to 1.03) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal non procedure related MI at 4.9years; Group 1: 308/5006, Group 2: 243/4995; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal non procedure related MI at 4.9years; HR 0.78 (95%CI 0.66 to 0.93) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 4.9 years; Group 1: 0/5006, Group 2: 0/4995; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Rhabdomyolysis at 4.9 years; Group 1: 0/1505, Group 2: 0/1602; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 4.9 years; Group 1: 113/3324, Group 2: 112/3225; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: All-cause mortality at 4.9 years; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from CHD at 4.9 years; Group 1: 127/5006, Group 2: 101/4995; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with CKD: Persisitent elevation in ALT and/or AST (two measurement >3 ULN 4-10 days apart) at 4.9 years; Group 1: 1/1505, Group 2: 22/1602; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Persisitent elevation ALT and/or AST at 4.9 years; Group 1: 8/3324, Group 2: 38/3225; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Non-fatal stroke at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Lemos 2003**[829]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1677)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3-4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-PCI
Subgroup analysis within study	Not applicable:
Inclusion criteria	Undergone first succesful PCI (defined as residual stenosis <50% and absence of in-hospital post-procedure MI, repeated revascularisation or death), fulfillment of at least 1 of the following criteria: total cholesterol 135-270 mg/dL (3.5 to 7.0 mmol/l) with fasting triglycerides <540 to <400 mg/dL; total cholesterol <212 mg/dL (5.5 mmol/l) for patients whose lipids levels were measured between 24 hours and 4 weeks after an episode of MI; total cholesterol <232 mg/dL (6.0 mmol/l) for patients with diabetes.
Exclusion criteria	Previous PCI or CABG, high blood pressure (>180/100 mmHg) despite drug treatment, poor left ventricular function (LVEF <30%), severe noncoronary heart disease, severe renal dysfunction (serum creatinine >1.8mg/dL [160 micromol/litre]), obesity (BMI>30kg/m²), malignant or other disease resulting in decreased life expectancy.
Recruitment/selection of patients	Between April 1996 and October 1998, patients were recruited from 77 referral centres in Europe, Canada and Brazil.
Age, gender and ethnicity	Age - Other: Mean; fluvastatin 60 years, placebo 60 years. Gender (M:F): No overall male/female ratio; fluvastatin 709/135, placebo 691/142. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean (mmol/l); fluvastatin 5.2, placebo 5.2. Baseline LDL-cholesterol mean (mmol/l); fluvastatin 3.4, placebo 3.4. LDL-cholesterol at 6 weeks mean (mmol/); fluvastatin 2.5, placebo 3.8. Diabetes (%); fluvastatin 14, placebo 10 (significant p<0.05).
Indirectness of population	No indirectness
Interventions	(n=844) Intervention 1: Medium intensity statin - Fluvastatin 80 mg. Fluvastatin 80 mg/day (Lescol, Novartis Pharma). Duration 3-4 years. Concurrent medication/care: Not reported but stated that groups well matched (n=833) Intervention 2: Placebo. N/A. Duration 3-4 years. Concurrent medication/care: Not reported but stated that groups well matched
Funding	Study funded by industry (Novartis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 80 MG versus PLACEBO

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis CK>10 times normal at 3-4 years; Group 1: 0/844, Group 2: 3/833; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3-4 years; Group 1: 35/844, Group 2: 49/833; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Cardiac death at 3-4 years; Group 1: 13/844, Group 2: 24/833; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Transaminases >3 times normal level on 2 consecutive occasions at 3-4 years; Group 1: 10/844, Group 2: 3/833; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Lemos 2013**[827]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=79)
Countries and setting	Conducted in Brazil; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Nephrology clinic
Stratum	Adults with CKD: CKD
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged <18 years with CKD and followed for at least 3 months by nephrologist.
Exclusion criteria	Chronic inflammatory diseases, active malignancy, HIV, viral hepatitis, use of steroids.
Recruitment/selection of patients	From nephrology clinic.
Age, gender and ethnicity	Age - Mean (SD): Statin 58.4 (8.7) years, no treatment 57.4 (12.7) years. Gender (M:F): 86/60. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: People without autoimmune disease 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness

Interventions	(n=38) Intervention 1: High intensity statin - Rosuvastatin 10 mg. Rosuvastatin 10 mg/day. Duration 2 years. Concurrent medication/care: Standard care for CKD; ACE inhibitors, diuretics, beta blockers, calcium channel blockers (n=41) Intervention 2: Placebo. No treatment. Duration 2 years. Concurrent medication/care: Standard care for CKD; ACE inhibitors, diuretics, beta blockers, calcium channel blockers
Funding	Study funded by industry (Genzyme Corporation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 10 MG versus PLACEBO Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with CKD: LDL-cholesterol at 2 years; Group 1: mean 2.03 mmol/l (SD 1.15); n=22, Group 2: mean 2.5 mmol/l (SD 0.7); n=29; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Meade 1999[949] (Collins 2003,[338] Collins 2004,[339] Armitage 2005,[108] Anon 2002[26])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20563)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Prior MI: 41%. History of coronary disease: 24%. No history of coronary disease: 35%.
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/l were eligible provided they were considered to be at substantial 5-year risk of death from CHD because of a past medical history of: (i) coronary disease (MI, unstable or stable angina, CABG, or angioplasty); or (ii) occlusive disease of non-coronary arteries (non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis [for example, intermittent claudication], carotid endarterectomy, other arterial surgery or angioplasty); or (iii) diabetes mellitus (whether type 1 or type 2); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories). No upper limit of blood cholesterol concentration for inclusion was imposed since there were people (such as those who had not previously had a MI, or were female or elderly) in whom many clinicians were substantially uncertain as to the benefits of lowering even an 'elevated' cholesterol. But, anyone in whom statin therapy was considered by their own doctor to be clearly indicated was not to be randomised.
Exclusion criteria	Chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of impaired renal function; inflammatory muscle disease or evidence of muscle problems; concurrent treatment with cyclosporine, fibrates, of high dose niacin; child bearing potential; severe heart failure; some life-threatening condition other than vascular disease or diabetes; or conditions that might limit long-term compliance.

Recruitment/selection of patients	Recruited from 69 UK hospitals. Randomisation between July 1994 and May 1997. Run-in phase: 4 weeks of placebo (to allow review of liver enzymes, creatinine, and creatine kinase by the central lab before starting any simvastatin) followed by 4-6 weeks of a fixed dose of simvastatin 40 mg/day (to allow a prerandomisation assessment of the LDL-cholesterol lowering responsiveness of each individual).
Age, gender and ethnicity	Age - Mean (SD): 64.0 (8.4) years. Gender (M:F): 15454/5082. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline concentration, mmol/l (of patients subsequently randomised, prior to any statin treatment); total cholesterol: 5.9, LDL-cholesterol: 3.4. Average concentrations during follow up: total cholesterol: simvastatin: 4.2, placebo: 5.4; LDL-cholesterol: simvastatin: 2.3, placebo: 3.3. Diabetes: 29%. Hypertension: 41%. Prior MI: 41%. History of coronary disease: 24%. No history of coronary disease: 35%.
Indirectness of population	No indirectness
Interventions	(n=10269) Intervention 1: Medium intensity statin - Simvastatin 40 mg. Simvastatin 40 mg/day. Until spring 1998, patients prescribed non-study statins were routinely advised to stop their simvastatin or placebo tablets, but subsequently that policy was changed so that non-study statin regimens of up to the equivalent, in lipid-lowering potency, of about 40 mg/day simvastatin could be added to the study simvastatin or placebo tablets. About 1/3 of patients taking non-study statins continued with their study tablets. Duration 5 years. Concurrent medication/care: Aspirin or another antiplatelet: 63%; oral anticoagulant: 5%; nitrate: 31%; beta blocker: 26%; calcium antagonist: 30%; ACE inhibitor: 20% (n=10267) Intervention 2: Placebo. Matching placebo. Until spring 1998, patients prescribed non-study statins were routinely advised to stop their simvastatin or placebo tablets, but subsequently that policy was changed so that non-study statin regimens of up to the equivalent, in lipid-lowering potency, of about 40 mg/day simvastatin could be added to the study simvastatin or placebo tablets. About 1/3 of patients taking non-study statins continued with their study tablets. Duration 5 years. Concurrent medication/care: Aspirin or another antiplatelet: 63%; oral anticoagulant: 5%; nitrate: 31%; beta blocker: 26%; calcium antagonist: 30%; ACE inhibitor: 20%

Funding	Academic or government funding (UK Medical Research Council, the British Heart Foundation, Merck, Roche)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome: Non-fatal MI at 5 years; Group 1: 357/10269, Group 2: 574/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome: Non-fatal stroke at 5 years; Group 1: 348/10269, Group 2: 466/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome: Any stroke at 5 years; Group 1: 444/10269, Group 2: 585/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Any stroke (diabetes group) at 5 years; Group 1: 149/2978, Group 2: 193/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome: CK >3 times ULN at 5 years; Group 1: 11/10269, Group 2: 6/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: CK >3 times ULN (diabetes group) at 5 years; Group 1: 4/2978, Group 2: 2/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome: All-cause mortality at 5 years; Group 1: 1328/10269, Group 2: 1507/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome: Vascular death (coronary, stroke, other vascular) at 5 years; Group 1: 781/10269, Group 2: 937/10267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome: ALT >4 times ULN at 5 years; Group 1: 42/10269, Group 2: 32/10267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: ALT >4 times ULN (diabetes group) at 5 years; Group 1: 14/2978, Group 2: 11/2985; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:New onset diabetes at 5 years
- Actual outcome: Development of new diabetes at 5 years; Group 1: 335/7291, Group 2: 293/7282; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Mercuri 1996[955]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=305)
Countries and setting	Conducted in Italy; Setting: CAIUS study. Primary care (lipid clinics)
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Carotid artery lesion detected by quantitative B-mode ultrasound imaging; fasting lipid profiles using standard procedures approved by the European Society of Arthersclerosis.
Stratum	Adults without established CVD : Men and women with isolated, moderate elevation of low-density lipoprotein cholesterol and ultrasinographic evidence of early carotid artery atherosclerosis, and who were asymptomatic for cardiovascular diseases.
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, 45 to 65 years old with moderately elevated LDL cholesterol (three baseline determinations of LDL cholesterol between 3.88 and 6.47 mmol/L and triglycerides level <2.82 nmol/L), free of symptoms and/or signs of coronary artery disease, and at least 1 carotid artery lesion detected by quantitative B-mode ultrasound imaging.
Exclusion criteria	Persistent liver function abnormalities, other serious medical conditions, and regular use of lipid-lowering agents, anticoagulants, and calcium antagonists.
Recruitment/selection of patients	Patients were screened in 7 lipid clinics. Eligible participants were enrolled in a 6-week single blind run-in period in which they were treated with placebo and advised to follow a low fat diet. After an additional evaluation of lipid values to confirm their eligibility, patients were then randomised.
Age, gender and ethnicity	Age - Mean (SD): 55.0 (5.99) years. Gender (M:F): 53%/47%. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Family history of CVD (Overall 45% of participants had a family history of CVD - but no subgroup analysis was conducted). 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline: Total cholesterol mmol/L: 6.72 (SD 0.57) (Pravastatin); 6.80 (SD 0.63) (Placebo); LDL cholesterol mmol/L: 4.66 (SD 0.49) (Pravastatin); 4.71 (SD 0.53) (Placebo); Follow-up: Total cholesterol mmol/L: mean difference -1.01 (SEM 0.08) (Pravastatin); 0.18 (SEM 0.07) (Placebo); LDL cholesterol mmol/L: -1.03 (SEM 0.07) (Pravastatin); 0.09 (SEM 0.06) (Placebo); No baseline information was presented on the % of people with diabetes, MI, stroke, or any other CV event
Indirectness of population	No indirectness
Interventions	(n=151) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg once a day. Duration 3 years. Concurrent medication/care: Not reported (n=154) Intervention 2: Placebo. Placebo manufactured to exactly resemble pravastatin. Duration 3 years. Concurrent medication/care: Not reported
Funding	Study funded by industry (Independent research grants provided by Bristol-Myers Squibb, and in part by a grant from the Italian National Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 3 years; Group 1: 1/151, Group 2: 2/154; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5

	years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Mok 2009[968]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=227)
Countries and setting	Conducted in Hong Kong (China); Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Mild to moderately elevated LDL-cholesterol
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged between 36 and 75 years, any MCA stenosis as detected by transcranial doppler, free of stroke or TIA and CHD, ≥1 risk factors for atherosclerosis, for example, diabetes mellitus, hypertension or smoking, mild to moderately elevated fasting LDL-cholesterol of 3.0-5.0 mmol/l.
Exclusion criteria	Known history of MI, angina, atrial fibrillation, CHF, serum triglyceride >4.5 mmol/l, ALT >20% ULN, elevated creatinine kinase, creatinine level >180 micromol/litre, women of child bearing age, patients already on lipid lowering drugs, known allergy to statins, presence of neurodegenerative diseases (for example, Alzheimer's disease), limited life expectancy of <2 years, contradictions to MRI, for example, metal implants.
Recruitment/selection of patients	Patients recruited between 1996 and 2000 at 3 regional hospitals in Hong Kong.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 63.0 (14.0) years, placebo 62.5 (13.0) years. Gender (M:F): No overall male/female; simvastatin 60/40, placebo 60/43. Ethnicity: Chinese
Further population details	1. Black and minority ethnic groups: Chinese 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under 4. People with a family history of CVD: Not applicable / Not

	stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean mmol/l; simvastatin 5.85, placebo 5.87. End of study total cholesterol mean mmol/l; simvastatin 4.46, placebo 5.88. Baseline LDL-cholesterol mean mmol/l; simvastatin 3.92, placebo 3.89. End of study total cholesterol mean mmol/; simvastatin 2.49, placebo 3.77. Diabetes (%); simvastatin 92.2, placebo 89.0.
Indirectness of population	No indirectness
Interventions	(n=113) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 2 years. Concurrent medication/care: Antihypertensives 77.7%, oral hypoglycaemics 75.7%, antiplatelet agents 15.5% (n=114) Intervention 2: Placebo. N/A. Duration 2 years. Concurrent medication/care: Antihypertensives 75%, oral hypoglycaemics 79%, antiplatelet agents 19%
Funding	Study funded by industry (Merck Sharp and Dohme Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal stroke at 5 years
- Actual outcome for Adults without established CVD : Non-fatal stroke at 2 years; Group 1: 3/113, Group 2: 4/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis CK>10 times normal at 2 years; Group 1: 0/113, Group 2: 0/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at 2 years; Group 1: 0/113, Group 2: 7/114; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults without established CVD : Transaminases >3 times normal level at 2 years; Group 1: 0/113, Group 2: 0/114; Risk of bias: Low; Indirectness of

outcome: No indirectness Protocol outcome 5: LDL-cholesterol reduction at 1 year - Actual outcome for Adults without established CVD : LDL-cholesterol at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Nakamura 2006[998] (Nakamura 2007,[997] Kushiro 2009[801])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=8214)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Total cholesterol concentration 5.69-6.98 mmol/l; serum lipids were measured at a central laboratory
Stratum	Adults without established CVD : Adults with hypercholesterolaemia and no history of CHD or stroke
Subgroup analysis within study	Not applicable: Patients were stratified according to sex, age, and medical institution; post hoc analysis was also conducted in patients with hypertension (n=3277) (Kushiro 2009)
Inclusion criteria	Men and post-menopausal women aged 40-70 years with a bodyweight of 40 kg or more and hypercholesterolaemia.
Exclusion criteria	Familial hypercholesterolaemia and a history of CHD or stroke (the authors stated that other exclusion criteria have been reported in a previous publication).
Recruitment/selection of patients	Participants were enrolled between February 1994 and March 1999.
Age, gender and ethnicity	Age - Mean (SD): 58.2(7.3) and 58.4 (7.2) years. Gender (M:F): 32%/68%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mmol/l; 6.27 (0.31) in both treatment groups. LDL-cholesterol mean (SD) mmol/l; 4.05 (0.45) pravastatin + diet and 4.05 (0.45) diet only; the authors stated that after 5 years, total cholesterol was reduced by 11.5% in the pravastatin + diet groups versus 2.1% in the diet alone group; LDL-cholesterol was reduced by 18% and 3.2% in the 2 groups, respectively. At baseline 21% of participants had diabetes. No other details on percentage of people with prior MI, or stroke, or any other CV event were presented. 26% were taking calcium-channel blockers, 12/13% were taking ACE inhibitors/ARB, and 8% were taking beta blockers
Indirectness of population	No indirectness
Interventions	(n=3866) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day + diet. Duration mean 5.3 years. Concurrent medication/care: Diet (following the National Cholesterol Education Program step 1 diet) (n=3966) Intervention 2: Placebo. Diet only. Duration mean 5.3 years. Concurrent medication/care: Diet (following the National Cholesterol Education Program step 1 diet). Mild hypolipidaemidic drugs (for example, y-oryzanol, riboflavin butyrate, pantethine) could also be prescribed.
Funding	Study funded by industry (Funds were provided by the Japanese Ministry of Health, Labor and Welfare for the first 2 years of the study, and thereafter the study was funded by Sankyo Co. Ltd.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : Total mortality at 5.3 years; HR 0.72 (95%CI 0.51 to 1.01) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults without established CVD : Cardiovascular death at 5.3 years; HR 0.63 (95%CI 0.3 to 1.33) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 5.3 years; Group 1: 16/3866, Group 2: 30/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness

- Actual outcome for Adults without established CVD : Fatal and non-fatal MI at 5.3 years; HR 0.52 (95%CI 0.29 to 0.94) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: Non-fatal stroke at 5 years - Actual outcome for Adults without established CVD : Stroke at 5.3 years; Group 1: 50/3866, Group 2: 62/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Stroke at 5.3 years; HR 0.83 (95%CI 0.57 to 1.21) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: All-cause mortality at 5 years - Actual outcome for Adults without established CVD : Total mortality at 5.3 months; Group 1: 55/3866, Group 2: 79/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 6: CV mortality at 5 years - Actual outcome for Adults without established CVD : Cardiovascular death at 5.3 years; Group 1: 11/3866, Group 2: 18/3966; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults without established CVD : New onset diabetes at 5.3 years; Group 1: 172/3013, Group 2: 164/3073; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Nicholls 2011[1023]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1385)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with CAD
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Age 18 to 75 years, had at least 1 vessel with 20% stenosis on clinically indicated coronary angiography and a target vessel for imaging with less than 50% obstruction. Patients who had not been treated with a statin in the preceding 4 weeks were required to have an LDL-cholesterol level at entry >2.6 mmol/l; those who had received such treatment were required to have a level >2.1 mmol/l.
Exclusion criteria	Patients who had received intensive lipid-lowering therapy for >3 months in the previous year or had uncontrolled hypertension, CHF, renal dysfunction, or liver disease.
Recruitment/selection of patients	Recruited from 208 centres from Jan 2008 to June 2009. Run-in period: 2-week treatment with half-maximal dose of either atorvastatin or rosuvastatin.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin: 57.9 (8.5) years, rosuvastatin: 57.4 (8.6) years. Gender (M:F): Atorvastatin; 386/133, rosuvatsatin; 379/141. Ethnicity: White 96%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline total cholesterol mean mmol/l; atorvastatin 5.00, rosuvastatin 5.01. During treatment total choloesterol mean mmol/l; atorvastatin 3.73, rosuvastatin 3.60. LDL-cholesterol mean mmol/l; atorvastatin: 1.82, rosuvastatin 1.62. Diabetes; atorvastatin 16.8%, rosuvastatin 13.8%. Hypertension; atorvastatin 70.7%, rosuvastatin 70.0%. Previous MI; atorvastatin 26.4%, rosuvastatin 22.5%. Previous PCI; atorvastatin 21.6%; rosuvastatin, 25.2%. Prior statin use; atorvastatin 61.5%, rosuvastatin 58.3%.
Indirectness of population	No indirectness
Interventions	(n=691) Intervention 1: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. Duration 2 years. Concurrent medication/care: Antiplatelet agent: 97.9%; beta blocker: 61.1%; ACE inhibitor: 44.5%; ARBs: 15.8% (n=694) Intervention 2: High intensity statin - Rosuvastatin 40 mg. Rosuvastatin 40 mg/day. Duration 2 years. Concurrent medication/care: Antiplatelet agent: 97.5%; beta blocker: 60.6%; ACE inhibitor: 43.5%; ARBs: 16.7%
Funding	Study funded by industry (AstraZeneca pharmaceutical)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 80 MG versus ROSUVASTATIN 40 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 2 years; Group 1: 11/689, Group 2: 11/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 2 years; Group 1: 2/689, Group 2: 3/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : CK >10 ULN at 2 years; Group 1: 4/668, Group 2: 1/668; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Rhabdomyolysis at 2 years; Group 1: 0/689, Group 2: 0/691; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 2 years; Group 1: 2/689, Group 2: 2/691; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : AST >3 ULN at 2 years; Group 1: 11/668, Group 2: 3/668; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : ALT >3 ULN at 2 years; Group 1: 14/668, Group 2: 5/668; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 2 years; Group 1: mean 1.82 mmol/l (SD 0.59); n=689, Group 2: mean 1.62 mmol/l (SD 0.59); n=694; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Nissen 2005[1033] (Nissen 2005,[1031] Nissen 2005[1030])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=502)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographically documented CAD
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	Angiographic evidence of CAD (stenosis of at least 20%), LDL-cholesterol level of 125 to 120 mg/dL after statin washout period of 4 to 8 weeks.
Exclusion criteria	None stated.
Recruitment/selection of patients	Recruited from 34 centres; patients with clinical indication for angiography.
Age, gender and ethnicity	Age - Other: Mean; atorvastatin 80 mg; 55.8 years, pravastatin 40 mg; 56.6 years. Gender (M:F): 72%/28%. Ethnicity: White; 89%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Indirectness of population	No indirectness
Interventions	(n=249) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg. Duration 18 months. Concurrent medication/care: Not reported (n=253) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 18 months. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 18 months; Group 1: mean 2.58 mmol/l (SD 0.52); n=249, Group 2: mean 2.09 mmol/l (SD 0.52); n=253; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Pedersen 2005[1074]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=8888)
Countries and setting	Conducted in Denmark, Finland, Iceland, Netherlands, Norway, Sweden; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 4.8 years (median)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Post-MI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≤80 years; history of a definite MI who qualified for statin therapy according to national guidelines at the time of recruitment.
Exclusion criteria	Any known contraindications to statin therapy; previous intolerance to statins in low or high doses; liver enzyme >2 times ULN; pregnancy or breastfeeding; nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled hypothyroidism; plasma triglyceride levels >6.8 mmol/l; CHF; haemodynamically important valvular heard disease; gastrointestinal conditions affecting absorption of drugs; treatment with other drugs that seriously affect the pharmacokinetics of statins; treatment with other lipid-lowering drugs; previously treated with statins who already had titration to a dose higher than the equivalent of 20 mg/day of simvastatin.
Recruitment/selection of patients	Recruited from 190 ambulatory cardiology and private specialist centres, from March 1999 to March 2001. Records of patients previously treated at the centres were screened for the main eligibility criteria. Potentially eligible patients were invited for a screening visit.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 61.6 (9.5) years; atorvastatin 61.8 (9.5) years. Gender (M:F): 7187/1701. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline cholesterol, mg/dL (SE): LDL-cholesterol; simvastatin 121.4 (0.5), atorvastatin 121.6 (0.5). Total cholesterol; simvastatin 195.9 (0.6), atorvastatin 196.8 (0.6). HDL-cholesterol; simvastatin 46.1 (0.2), atorvastatin 46.0 (0.2). Cholesterol at 5 years mg/dL (SE): LDL-cholesterol: simvastatin 99.8 (0.9), atorvastatin 80.0 (1.0). Total-cholesterol: simvastatin 176.8 (1.0), atorvastatin 153.4 (1.3). HDL-cholesterol: simvastatin 50.6 (0.5), atorvastatin 50.1 (0.5). Diabetes: simvastatin 12.1%, atorvastatin 12.0%. Aspirin: simvastatin 79.5%, atorvastatin 78.7%. Warfarin or dicoumarol: simvastatin 12.6%, atorvastatin 12.6%. Beta blockers: simvastatin 73.7%, atorvastatin 76.1%. Calcium antagonists: simvastatin 18.9%, atorvastatin 19.9%. ACE inhibitors: simvastatin 30.7%, atorvastatin 29.2%. ARBs: simvastatin 6.1%, atorvastatin 5.9%.
Indirectness of population	No indirectness
Interventions	(n=4449) Intervention 1: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. If, at 24 weeks, total cholesterol >190 mg/dL (5.0 mmol/l), the dose of simvastatin could be increased to 40 mg/day. At the end of the study, 1034 (23%) were prescribed simvastatin 40 mg/day. Duration 4.8 years. Concurrent medication/care: Aspirin: 79.5%. Warfarin or dicoumarol: 12.6%. Beta blockers: 73.7%. Calcium antagonists: 18.9%. ACE inhibitors: 30.7%. ARBs: 6.1%. Pre-randomisation statin. Simvastatin: 50.1%. Atorvastatin: 11.5%. Pravastatin: 9.7%. Other statins: 4.5%. (n=4439) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg/day. The dose of atorvastatin could be decreased to 40 mg/day for adverse events. At 24 weeks 250 (6%) people had the dose reduced to 40 mg/day. At the end of the study, 587 (13%) people had the dose reduced to 40 mg/day. Duration 4.8 years. Concurrent medication/care: Aspirin: 78.7%. Warfarin or dicoumarol: 12.6%. Beta blockers: 76.1%. Calcium antagonists: 19.9%. ACE inhibitors: 29.2%. ARBs: 5.9%. Pre-randomisation statin. Simvastatin: 50.3%. Atorvastatin: 11.2%. Pravastatin: 9.4%. Other statins: 4.2%.
Funding	Study funded by industry (Study sponsored by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 20 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 4.8 years; Group 1: 321/4449, Group 2: 267/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Fatal or non-fatal stroke at 4.8 years; Group 1: 174/4449, Group 2: 151/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with established CVD : Myopathy defined as CPK>10 x ULN at 2 consecutive measurements with muscle symptoms at 4.8 years; Group 1: 0/4449, Group 2: 0/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 4.8 years; Group 1: 374/4449, Group 2: 366/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: CV mortality at 5 years
- Actual outcome for Adults with established CVD : CV mortality at 4.8 years; Group 1: 218/4449, Group 2: 223/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse event: Myalgia at 5 years
- Actual outcome for Adults with established CVD : Myalgia at 4.8 years; Group 1: 51/4449, Group 2: 97/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with established CVD : ALT>3 x ULN at 2 consecutive measurements at 4.8 years; Group 1: 5/4449, Group 2: 43/4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 4.8 years; Group 1: mean 2.58 mmol/l (SD 0.52); n=4449, Group 2: mean 2.09 mmol/l (SD 0.52); n=4439; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Pitt 1995**[1094]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=408)
Countries and setting	Conducted in Canada, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The authors stated that the angiographic protocol and quantitative analysis methodology had been previously described. Other methods were also reported.
Stratum	Adults with established CVD : Patients with mild to moderate hypercholesterolemia and coronary artery disease
Subgroup analysis within study	Not applicable
Inclusion criteria	CABG evidenced by 1 or more stenoses ≥50% or recent MI or coronary angioplasty; average LDL-cholesterol concentration ≥130 mg/dL but <190 mg/dL and triglyceride levels ≤350 mg/dL despite adherence to a fat restricted diet for a minimum of 4 weeks.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Mean 57 years. Gender (M:F): 38%/62%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear (51/206 (25%) patients in the pravastatin group and 56/202 (28%) patients in the placebo group had a family history of atherosclerosis, but no subgroup analysis was conducted). 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated /

	Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol and LDL-cholesterol were not reported separately for each treatment group. The authors stated that in the pravastatin group, the average percent change from baseline was -19% for total cholesterol and -28% for LDL-cholesterol; in the placebo group the average percent change from baseline was +2% for total cholesterol and +1% for LDL-cholesterol; At baseline 21% of participants had prior MI, 27% had prior angioplasty and 2% had prior CABG. No information was presented on percentage of people with diabetes
Indirectness of population	No indirectness
Interventions	(n=206) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 3 years. Concurrent medication/care: Not reported (n=202) Intervention 2: Placebo. Placebo. Duration 3 years. Concurrent medication/care: Not reported
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3 years; Group 1: 7/206, Group 2: 16/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 0/206, Group 2: 2/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total deaths at 3 years; Group 1: 4/206, Group 2: 6/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Cardiac death at 3 years; Group 1: 2/206, Group 2: 2/202; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Raggi 2005[1122]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=615)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Calcium volume score, LDL-cholesterol level
Stratum	Overall: Hyperlipidaemic women
Subgroup analysis within study	Not applicable
Inclusion criteria	Post-menopausal women with calcium volume score ≥30. Lipid criteria; LDL-cholesterol level ≥ 3.4 mmol/l for women with CHD, or ≥2 risk factors and a 10 year risk of CVD of 10% to 20%; LDL-cholesterol ≥4.1 mmol/l for patients with ≥2 CHD risk factors and 10 year CVD risk of <10%; or patients with 0 to 1 risk factors.
Exclusion criteria	Intolerance to statins, for example, hypersensitivity or hepatic dysfunction with aspartate transaminase (AST) or alanine transaminase (ALT) levels ≥1.5 x ULN at any time between screening and randomisation, treatment with lipid-lowering drugs other than HRT within 3 months of screening, evidence of secondary hyperlipidemia (as in nephrotic syndrome), renal dysfunction (creatinine ≥1.5 mg/dl), uncontrolled type 1 or type 2 diabetes mellitus (defined by HbA1c >10%), MI <6 months before screening, uncontrolled hypothyroidism (defined by thyroid stimulating hormone >1.5 times ULN) and plasma triglyceride levels >6.8 mmol/l).
Recruitment/selection of patients	Recruited from 96 sites, subjects underwent initial screening visit.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin; 64.2 (6.5) years, pravastatin 64.5 (6.0) years. Gender (M:F): 0:475. Ethnicity: 92% Caucasian

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear (92% Caucasian). 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women
Indirectness of population	No indirectness
Interventions	(n=257) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg. Duration 1 year. Concurrent medication/care: Not reported (n=218) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome: Rhandomyolysis at 1 year; Group 1: 0/257, Group 2: 1/218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome: ALT/AST > 3 times upper limit normal at 1 year; Group 1: 0/257, Group 2: 7/218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year
- Actual outcome: LDL-cholesterol at 1 year; Group 1: mean 3.34 mmol/l (SD 0.8); n=257, Group 2: mean 2.38 mmol/l (SD 0.93); n=218; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Ridker 2008[1153] (Ridker 2007,[1154] Ridker 2008,[1152] Kones 2009,[777] Ridker 2009,[1156] Everett 2010,[483] Mora 2010,[974] Ridker 2010,[1155] Albert 2011,[71] Hsia 2011,[681] Ridker 2012[1157])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4631)
Countries and setting	Conducted in Multiple countries; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.9 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Measurement of lipids levels, high-sensitivity C-reactive protein levels, hepatic and renal function, blood glucose levels, and glycated haemoglobin values were performed in a central laboratory
Stratum	Adults without established CVD : Apparently healthy men and women with low-density lipoprotein levels <130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/dL or higher
Subgroup analysis within study	Unclear: Stratified according to centre; pre-specified subgroup analyses were performed according to the presence or absence of major CV risk factors. Subgroup analyses were also conducted for a number of other variables, including sex (Mora 2010), LDL-cholesterol levels (Hsia 2011), ethnicity (Albert 2011), diabetes risk factor (Ridker 2012), and baseline renal function (Ridker 2010).
Inclusion criteria	Men 50 years of age or older and women 60 years of age or older without a history of CVD; with an LDL-cholesterol level <130 mg/dL and a high sensitivity C-reactive protein level of 2.0 mg/dL or more; willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level <500 mg/dL.
Exclusion criteria	Previous or current use of lipid-lowering therapy, current use of post-menopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level >2 times ULN), a creatine kinase level >3 times upper limit of the normal range, a creatinine level that was higher than 2.0 mg/dL, diabetes, uncontrolled hypertension, cancer within 5 years before enrollment, uncontrolled hypothyroidism, and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Patients with

	inflammatory conditions such as severe arthritis, lupus or inflammatory bowel disease were also excluded as well as patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.
Recruitment/selection of patients	All potentially eligible participants underwent a 4-week placebo run-in phase; only those who successfully completed the run-in phase were enrolled. Between Feb 2003 and Dec 2006, 89,890 people were screened.
Age, gender and ethnicity	Age - Mean (SD): 68 (SD 11) years. Gender (M:F): 62%/38%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear (Subgroup analysis was conducted for White, Non-white, Black and Hispanic participants (Albert 2011) (data not extracted)). 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear (Subgroup analysis conducted for =<65 years/>65 years for the primary outcome only: the combination of nonfatal MI, nonfatal stroke, and arterial revascularisation, hospitalisation for unstable angina, or confirmed death from cardiovascular causes). 4. People with a family history of CVD: Not applicable / Not stated / Unclear (12% of participants had a family history of CHD; subgroup analysis was conducted for the primary outcome only: the combination of nonfatal MI, nonfatal stroke, and arterial revascularisation, hospitalisation for unstable angina, or confirmed death from cardiovascular causes). 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Subgroup analysis was conducted separately for women and men (see Mora et al. 2010) (data not extracted)).
Extra comments	. Baseline total cholesterol (mg/dL): median (IQR) 186 (168-200) in rosuvastatin group and 185 (169-199) in placebo group. LDL-cholesterol (mg/dL): median (IQR) 108 (94-119) in both groups (total cholesterol was not reported). At 48 months median (IQR) LDL-cholesterol was 55 (44-70) in rosuvastatin group and 109 (94-124) in the placebo group. At baseline, 12% had a family history of premature CHD, 42% had metabolic syndrome, and 17% were using aspirin. As per inclusion criteria, no patients were to have a history of CVD or diabetes.
Indirectness of population	Serious indirectness
Interventions	(n=8901) Intervention 1: High intensity statin - Rosuvastatin 20 mg. Rosuvastatin 20 mg/day. Duration Median 1.9 years. Concurrent medication/care: Not reported, other than 17% were taking aspirin (n=8901) Intervention 2: Placebo. Placebo. Duration Median 1.9 years. Concurrent medication/care: Not reported, other than 17% were taking aspirin

Funding	Study funded by industry (Societa Prodotti Antibiotici, Pfizer, Signam Tau, and AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years

- Actual outcome for Adults without established CVD : All-cause mortality at Median 1.9 years; HR 0.8 (95%CI 0.67 to 0.97) Reported; Risk of bias: Low; Indirectness of outcome:

Protocol outcome 2: Non-fatal MI at 5 years

- Actual outcome for Adults without established CVD : Non-fatal MI at Median 1.9 years; Group 1: 22/8901, Group 2: 62/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: MI at Median 1.9 years; Group 1: 8/1638, Group 2: 20/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: MI at Median 1.9 years; HR 0.4 (95%CI 0.17 to 0.9) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults without established CVD : Non-fatal MI at Median 1.9 years; HR 0.35 (95%CI 0.22 to 0.58) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal stroke at 5 years

- Actual outcome for Adults without established CVD : Non-fatal stroke at Median 1.9 years; Group 1: 30/8901, Group 2: 58/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: Stroke at Median 1.9 years; Group 1: 10/1638, Group 2: 14/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: Stroke at Median 1.9 years; HR 0.71 (95%CI 0.31 to 1.59) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults without established CVD : Non-fatal stroke at Median 1.9 years; HR 0.52 (95%CI 0.33 to 0.8) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years

- Actual outcome for Adults without established CVD : Rhabdomyolysis at Median 1.9 years; Group 1: 16/8901, Group 2: 10/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: Creatinine >100% increase from baseline at Median 1.9 years; Group 1: 3/1638, Group 2: 0/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 5 years

- Actual outcome for Adults without established CVD : All-cause mortality at Median 1.9 years; Group 1: 198/8901, Group 2: 247/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: All-cause mortality at Median 1.9 years; Group 1: 34/1638, Group 2: 61/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 5 years

- Actual outcome for Adults without established CVD : CV mortality at Median 1.9 years; Group 1: 45/8901, Group 2: 57/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event: Myalgia at 5 years

- Actual outcome for Adults with CKD: Muscular weakness, stiffness, or pain at Median 1.9 years; Group 1: 292/1638, Group 2: 303/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Adverse event:Liver (transaminases >3 times normal level) at 5 years

- Actual outcome for Adults without established CVD : ALT >3 times ULN at Median 1.9 years; Group 1: 23/8901, Group 2: 17/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with CKD: ALT >3 times ULN on consecutive visits at Median 1.9 years; Group 1: 2/1638, Group 2: 4/1629; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Adverse event:New onset diabetes at 5 years

- Actual outcome for Adults without established CVD : Newly diagnosed diabetes at Median 1.9 years; Group 1: 270/8901, Group 2: 216/8901; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 10: LDL-cholesterol reduction at 1 year

- Actual outcome for Adults with CKD: All-cause mortality at Median 1.9 years; HR 0.56 (95%CI 0.37 to 0.85) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with established CVD : LDL-cholesterol final values at 2 years; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at 5 years

Study	**Riegger 1999[1158]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=365)
Countries and setting	Conducted in Czech Republic, Germany; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Symptomatic CHD
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable symptomatic CHD (clinically diagnosed with exercise-ECG finding of >0.1 mV ST-segment depression), total cholesterol ≥250 mg/dL at first screening, LDL-cholesterol >160 mg/dL and triglycerides ≤300 mg/dL completion of 4 week cholesterol-lowering diet.
Exclusion criteria	PCI in 6 months prior to start of study, planned PCI or CABG, CHF NYHA III and IV, hypersensitivity or intolerance to HMG-CoA reductase inhibitors, therapy with non-registered drugs or participation in other experimental studies within 3 months of start of trial, diseased and conditions which could influence the pharmacokinetics or pharmacodynamics of the trial medication, for example,gastrointestinal diseases, liver and kidney diseases, AST and ALT >120% ULN, γ-GT, ALP, bilirubin and creatinine above 150% ULN, pregnant or breastfeeding women, women of child bearing age not using adequate contraception, non-permitted concomitant medication (probucol, digitalis, steroid hormones, antacids containing aluminium, immunosuppressive therapy, erythromycin, ketoconazole, para-aminosalicylic acid), medication abuse, drug abuse and/or alcohol abuse. Patients likely to be non-compliant were also excluded.
Recruitment/selection of patients	Multicentre trial conducted in the Czech Republic and Germany. Planning began in 1993.
Age, gender and ethnicity	Age - Mean (SD): Fluvastatin 59.4 (7.5) years, placebo 60.2 (7.2) years. Gender (M:F): Fluvastatin: 63%/37%, placebo:

	60%/40%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline total cholesterol mean mmol/l; fluvastatin 7.47, placebo 7.34. Total cholesterol at 1 year mean mmol/l; fluvastatin 6.17, placebo 6.98. Baseline LD- cholesterol mmol/l; fluvastatin 5.12, placebo 4.99. LDL-cholesterol at 1 year mmol/l; fluvastatin 3.74, placebo 4.6. Proportion with diabetes; fluvastatin 4.3%, placebo 6.7%. Prior to randomisation all patients underwent a 10 week run in period, the first 4 weeks on a lipid-lowering diet and the following 6 weeks receiving treatment with fluvastatin 40mg/day 'to assess the lipid-lowering effect'. Of the 572 patients entered into the lead-in period, 365 were randomised.
Indirectness of population	No indirectness
Interventions	(n=187) Intervention 1: Low intensity statin - Fluvastatin 40 mg. Fluvastatin 40 mg/day; if LDL-cholesterol decreased ≤30% at 6 weeks, dosage increased to 40 mg twice daily. Dose was increased for 85 patients (45.5%) according to the protocol. Duration 1 year. Concurrent medication/care: ACE inhibitors 18.7%, calcium antagonists 31.6%, beta blockers 23.0%, nitrates 52.9%, diuretics 7.5%, acetylsalicylic acid 43.9% (n=178) Intervention 2: Placebo. Placebo once daily; if LDL-cholesterol decreased ≤30% at 6 weeks, dosage increased to placebo twice daily. Duration 1 year. Concurrent medication/care: ACE inhibitors 21.9%, calcium antagonists 33.7%, beta blockers 18.6%, nitrates 59.0%, diuretics 5.6%, acetylsalicylic acid 40.4%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 1 year; Group 1: 0/187, Group 2: 1/178; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Elevation of CK at 1 year; Group 1: 0/187, Group 2: 1/178; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 5 years - Actual outcome for Adults with established CVD : CV mortality at 1 year; Group 1: 2/187, Group 2: 4/178; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Sacks 1996[1182] (Goldberg 1998,[563] Lewis 1998,[840] Lewis 1998,[841] Flaker 1999,[502] Plehn 1999,[1099] Tonelli 2003[1336])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=4159)
Countries and setting	Conducted in Canada, USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Criteria for a qualifying MI included typical symptoms and an elevated serum level of creatine kinase
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable: For the primary outcome (death from coronary disease or non-fatal MI) a number of subgroup analyses were undertaken, including sex, age, hypertension, diabetes, cholesterol level.
Inclusion criteria	Men and postmenopausal women (21 to 75 years of age) who had an acute MI between 3 and 20 months before randomisation, plasma total cholesterol levels less than 240 mg/dL, LDL-cholesterol levels of 115 to 174 mg/dL, fasting triglyceride fasting glucose levels of less than 350 mg/dL, fasting glucose levels of no more than 220 mg/dL, left ventricular ejection fractions of no less than 25%, and no symptomatic CHF.
Exclusion criteria	Participants with 2+ proteinuria or greater on routine dipstick testing or serum creatinine values more than 1.5 times ULN.
Recruitment/selection of patients	Patients were recruited from 80 participating centres between Dec 1989 and Dec 1991.
Age, gender and ethnicity	Age - Mean (SD): 59 (9) years. Gender (M:F): 86%/14%. Ethnicity: White: 92-93%; Other: 7-8% (no other details reported by study authors)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: People aged 75 years or under (Subgroup analysis was conducted in patients aged 65 to 75 years (Lewis et al. 1998), data not extracted). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women, subgroup analysis was conducted in postmenopausal women only (Lewis et al. 1998a), data not extracted).
Extra comments	Baseline: Total cholesterol mean (SD) mg/dL; 209 (17) pravastatin and placebo group have the same mean. LDL-cholesterol mean (SD) mg/dL; 139 (15) pravastatin and placebo group have the same mean. 5 year follow-up; authors stated that the LDL-cholesterol level was 28% lower in the pravastatin group compared to the placebo group; pravastatin lowered the mean LDL-cholesterol level by 32% (no other details were reported). At baseline 14% in active group and 15% in placebo group has diabetes, all patients had a MI. Other subgroup analysis conducted include revascularised patients (Flaker et al. 1999), persons with mild chronic renal insufficiency (Tonelli et al. 2003), women (Lewis et al. 1998), age (Lewis et al. 1998), and diabetic and glucose-intolerant participants (Goldberg et al. 1998)
Indirectness of population	No indirectness
Interventions	(n=2081) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 5 years. Concurrent medication/care: Patients continued to take all prescribed medication, for cardiac and other conditions that they had been receiving at baseline including; aspirin - 83%, beta blockers - 41%, nitrate - 32%, calcium-channel blocker - 40%, ACE inhibitor - 15%, diuretic agent - 11%, insulin - 2.4%, oral hypoglycemic agent - 5%, estrogen - 8.4% (n=2078) Intervention 2: Placebo. Placebo. Duration 5 years. Concurrent medication/care: Patients continued to take all prescribed medication, for cardiac and other conditions that they had been receiving at baseline including; aspirin - 83%, beta blockers - 39%, nitrate - 33%, calcium-channel blocker - 38%, ACE inhibitor - 14%, diuretic agent - 11%, insulin - 2.6%, oral hypoglycemic agent - 7%, estrogen - 10.3%)
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with CKD: All-cause mortality at 5 years; HR 0.81 (95%CI 0.61 to 1.08) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 5 years; Group 1: 135/2081, Group 2: 173/2078; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Non-fatal MI at 5 years; Group 1: 28/282, Group 2: 37/304; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Fatal or non-fatal MI at 5 years; Group 1: 65/844, Group 2: 90/867; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Fatal or non-fatal MI at 5 years; HR 0.73 (95%CI 0.52 to 1.01) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 5 years; Group 1: 54/2081, Group 2: 78/2078; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Stroke at 5 years; Group 1: 19/282, Group 2: 24/304; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Stroke at 5 years; Group 1: 29/844, Group 2: 46/867; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: Stroke at 5 years; HR 0.62 (95%CI 0.39 to 1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults with CKD: CK >10 ULN at 5 years; Group 1: 6/844, Group 2: 3/867; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 5 years; Group 1: 180/2081, Group 2: 196/2078; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with CKD: All-cause mortality at 5 years; Group 1: 86/844, Group 2: 111/867; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death from coronary heart disease at 5 years; Group 1: 96/2081, Group 2: 119/2078; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with type 2 diabetes: Death from coronary heart disease at 5 years; Group 1: 27/282, Group 2: 30/304; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults with CKD: Abnormalities on liver function test at 5 years; Group 1: 5/844, Group 2: 5/867; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:New onset diabetes at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Satoh 2009[1199]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CAD based on (i) typical chest pain (ii) exercise induced myocardial ischaemia (iii) angiography (iv) absence ACS last 3 months
Stratum	Adults with established CVD :
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable CAD and statin naive.
Exclusion criteria	Clinical signs of acute infection, severe renal failure or rheumatoid disease, malignant disorder or primary wasting disorder.
Recruitment/selection of patients	Consecutive patients.
Age, gender and ethnicity	Age - Mean (SD): 64.9 (10.1) years. Gender (M:F): 60:40. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: People with autoimmune disease 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Low intensity statin - Pravastatin 10 mg. Pravastatin 10 mg. Duration 1 year. Concurrent medication/care: Aspirin, ACE/ARB inhibitors, beta-blockers, calcium antagonists, nitrates (n=50) Intervention 2: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: Aspirin, ACE/ARB inhibitors, beta-blockers, calcium antagonists, nitrates
Funding	Academic or government funding (Japanese Ministry of Education, Science, Sports & Culture, Keiryokai Research Foundation, Open Translational Research Centre, Advanced Medical Science Centre, Iwate Medical University.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 10 MG versus ATORVASTATIN 10 MG Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.9 mmol/l (SD 0.74); n=50, Group 2: mean 2.56 mmol/l (SD 0.72); n=50; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Schmermund 2006[1212]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=471)
Countries and setting	Conducted in Germany, Russia, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiography
Stratum	Adults without established CVD : Without CVD (≥2 CV risk factors)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Triglycerides <400 mg/dL, (2) ≥2 CV risk factors (smoking, hypertension, diabetes, family history CVD, HDL-cholesterol <45 mg/dL, LDL-cholesterol ≥160 mg/dL) (3) the absence of high grade coronary stenoses (angiographically defined as ≥50% diameter lumen narrowing) by coronary angiography or a normal result of noninvasive exercise stress testing (4) CAC score according to Agatston method ≥30.
Exclusion criteria	Prior ischaemic heart disease, unstable angina, CHF, atrial fibrillation, type 1 diabetes, uncontrolled type 2 diabetes, treatment with lipid lowering drugs >4 weeks within 6 months study start.
Recruitment/selection of patients	Subjects screened at 55 sites in 3 countries.
Age, gender and ethnicity	Age - Mean (SD): Atorvastatin 80 mg; 61 (8) years, atorvastatin 10 mg; 62 (8) years. Gender (M:F): 217:149. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=236) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: Not reported (n=235) Intervention 2: High intensity statin - Atorvastatin 80 mg. Atorvastatin 80 mg. Duration 1 year. Concurrent medication/care: Not reported
Funding	Study funded by industry (Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus ATORVASTATIN 80 MG

Protocol outcome 1: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolysis at 1 year; Group 1: 0/233, Group 2: 0/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Myalgia at 5 years
- Actual outcome for Adults without established CVD : Myalgia at 1 year; Group 1: 5/233, Group 2: 7/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse event:Liver (transaminases >3 times normal level) at 5 years
- Actual outcome for Adults without established CVD : Transaminases > 3 times upper limit normal at 1 year; Group 1: 2/233, Group 2: 2/234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults without established CVD : LDL-cholesterol at 1 year; Group 1: mean 2.82 mmol/l (SD 0.72); n=233, Group 2: mean 2.25 mmol/l (SD 0.72); n=234; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Sever 2003[1233] (Sever 2004,[1234] Sever 2011[1232])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=10305)
Countries and setting	Conducted in Denmark, Finland, Iceland, Irish Republic, Norway, Sweden, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Median 3.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with untreated hypertension defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both, or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both.
Stratum	Adults without established CVD : Hypertensive patients who had average or lower-than-average cholesterol concentrations, and who had at least 3 other cardiovascular risk factors
Subgroup analysis within study	Stratified then randomised: Randomisation using the minimisation procedure; also pre-specified subgroup analyses by diabetes status, smoking, obesity, LVH, age, sex, vascular disease, renal dysfunction, and metabolic syndrome. Long-term follow-up analysis was also conducted in subjects recruited to the trial in the UK only (Sever et al. 2011) (data not extracted)
Inclusion criteria	Men, aged 55 years or older, with either untreated hypertension or treated hypertension, and not taking a statin or fibrate, patients had to have at least 3 of the following risk factors for CVD; left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, PAD, previous stroke or transient ischaemic attack, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, or premature family history of CHD.
Exclusion criteria	Previous MI, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 4.5 mmol/l, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening.

Recruitment/selection of patients	Most patients were recruited from family practice. Patients were recruited between Feb 1998 and May 2000.
Age, gender and ethnicity	Age - Mean (SD): 63 (8.5) years. Gender (M:F): 81%/19%. Ethnicity: 95% White
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged 75 years or under (Subgroup analysis in patients >60 and =<60 years on the primary end-point (non-fatal plus fatal CHD)). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Baseline total cholesterol mean (SD) mmol/l; 5.5 (0.8) in both treatment groups. Baseline LDL-cholesterol mean (SD) mmol/l; 3.4 (0.7) in both treatment groups. At end of follow-up: total cholesterol mean (SD) mmol/l; mean 4.21 (0.85) atorvastatin, 5.21 (0.91) placebo; LDL-cholesterol mean (SD) mmol/l: 2.32 (0.72) atorvastatin,3.27 (0.81) placebo. At baseline; 25% of people had diabetes, 10% had a previous stroke or transient ischaemic attack, 14% had left-ventricular hypertrophy, 14% had ECG abnormalities other than LVH, 5% had peripheral vascular disease and 4% had other relevant CVD.
Indirectness of population	No indirectness
Interventions	(n=5168) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration Median 3.3 years. Concurrent medication/care: Any lipid-lowering treatment other than a fibrate or a statin, in use before randomisation could be continued during the study (n=5137) Intervention 2: Placebo. Placebo. Duration Median 3.3. years. Concurrent medication/care: Any lipid-lowering treatment other than a fibrate or a statin, in use before randomisation could be continued during the study
Funding	Study funded by industry (Principally supported by Pfizer, and also funded by Servier Research Group, and Leo Laboratories)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO Protocol outcome 1: Non-fatal stroke at 5 years	

- Actual outcome for Adults without established CVD : Stroke (fatal and non-fatal) at Median 3.3 years; Group 1: 89/5168, Group 2: 121/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Stroke (fatal and non-fatal) at Median 3.3 years; HR 0.73 (95%CI 0.56 to 0.96) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years
- Actual outcome for Adults without established CVD : Rhabdomyolyisis at Median 3.3 years; Group 1: 1/5168, Group 2: 0/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at Median 3.3 years; Group 1: 185/5168, Group 2: 212/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : All-cause mortality at Median 3.3 years; HR 0.87 (95%CI 0.71 to 1.06) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years
- Actual outcome for Adults without established CVD : CV mortality at Median 3.3 years; Group 1: 74/5168, Group 2: 82/5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : CV mortality at Median 3.3 years; HR 0.9 (95%CI 0.66 to 1.23) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse event:New onset diabetes at 5 years
- Actual outcome for Adults without established CVD : Development of diabetes mellitus at Median 3.3 years; Group 1: 154/3910, Group 2: 134/3863; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Development of diabetes mellitus at Median 3.3 years; HR 1.15 (95%CI 0.91 to 1.44) Reported; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 6: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults without established CVD : LDL-cholesterol at Median 3.3 years; Group 1: mean 2.32 mmol/l (SD 0.72); n=5168, Group 2: mean 3.27 mmol/l (SD 0.81); n=5137; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Quality of life at 5 years

Study (subsidiary papers)	**Shepherd 1995[1249] (Freeman 2001[514])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=6595)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 4.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Detailed methods of assessment were reported in the paper
Stratum	Adults without established CVD : Men with moderate hypercholesterolemia and no history of MI
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis by age (<55 or ≥55 years), smoking status, and whether at least 2 of the following risk factors were present: smoking, hypertension, a history of chest pain or intermittent claudication, diabetes, and a minor ECG abnormality associated with CHD
Inclusion criteria	Men 45-64 years of age; fasting LDL-cholesterol level of at least 155 mg/dL (during second and third visits to clinic before randomisation) with at least one value of 174 mg/dL or above and one value of 232 mg/dL or below; no serious ECG abnormalities according to Minnesota code 1, 1-l, 5-l, or 7-1-l or arrhythmia such as atrial fibrillation; and no history of MI or other serious illness, although men with stable angina who had not been hospitalised with the previous 12 months were eligible.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Screening clinics were established in primary medical care facilities throughout the West of Scotland district. Participants were enrolled between September 1991 and May 1995
Age, gender and ethnicity	Age - Mean (SD): 55.2 (5.5) years. Gender (M:F): 100% male. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Baseline total cholesterol mean (SD) mg/dL; 272 (23) pravastatin, 272 (22) placebo. Baseline LDL-cholesterol mean (SD) mg/dL; 192 (17) for both groups. No other data were reported. At baseline 1% of participants has diabetes, 5% had angina, and 3% had intermittent claudication.
Indirectness of population	No indirectness
Interventions	(n=3302) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration 4.9 years. Concurrent medication/care: Dietary advice (n=3293) Intervention 2: Placebo. Placebo. Duration 4.9 years. Concurrent medication/care: Dietary advice
Funding	Study funded by industry (Supported by a grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults without established CVD : Non-fatal MI at 4.9 years; Group 1: 143/3302, Group 2: 204/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Adults without established CVD : Non-fatal MI at 4.9 years; HR 0.7 (95%CI 0.56 to 0.86) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults without established CVD : Non-fatal stroke at 4.9 years; Group 1: 40/3302, Group 2: 47/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults without established CVD : All-cause mortality at 4.9 years; Group 1: 106/3302, Group 2: 135/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness

- Actual outcome for Adults without established CVD : All-cause mortality at 4.9 years; HR 0.78 (95%CI 0.6 to 1) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults without established CVD : Death from all cardiovascular causes at 4.9 years; Group 1: 50/3302, Group 2: 73/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Death from all cardiovascular causes at 4.9 years; HR 0.68 (95%CI 0.47 to 0.97) Calculated – from logrank P-value; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 5: Adverse event: Myalgia at 5 years - Actual outcome for Adults without established CVD : Myalgia at 4.9 years; Group 1: 20/3302, Group 2: 19/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults without established CVD : Aspartate aminotransferase (>3 times the upper reference limits) at 4.9 years; Group 1: 26/3302, Group 2: 20/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD : Alanine aminotransferase (>3 times the upper reference limits) at 4.9 years; Group 1: 16/3302, Group 2: 12/3293; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults without established CVD : New onset diabetes at 4.9 years; Group 1: 75/2999, Group 2: 93/2975; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study (subsidiary papers)	**Shepherd 2002[1247] (Shepherd 2004[1245])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=5804)
Countries and setting	Conducted in Irish Republic, Netherlands, United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: Mean 3.2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Lipoprotein profiles were measured at the Centre for Disease Control certified central lipoprotein laboratory in Glasgow. A 12-lead ECG was recorded yearly.
Stratum	Adults with established CVD : Older men and women (70-82) with a history of, or risk factors for, vascular disease
Subgroup analysis within study	Not stratified but pre-specified: Subgroup analysis by smoking status, history of hypertension, sex, diabetes, and LDL- and HDL-cholesterol, and also gender and pre-existing disease
Inclusion criteria	Men and women aged 70-82 years with either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes; total cholesterol 4.0-9.0 mmol/l and triglycerides less than 6.0 mmol/l.
Exclusion criteria	Participants with poor cognitive function were excluded. Also, those who used less than 75%, or more than 120% of the placebo medication during a single-blind placebo period were excluded.
Recruitment/selection of patients	Participants were enrolled between Dec 1997 and May 1999. After screening, eligible patients entered a 4-week single-blind placebo period.
Age, gender and ethnicity	Age - Mean (SD): 75.4 (3.3) years in pravastatin group, 75.3 (3.4) years in placebo group. Gender (M:F): 48%/52%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: People aged over 75 years (All people included in this trial were between 70-82 years of age). 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Women (Men and women; subgroup analysis was conducted in women).
Extra comments	Baseline total cholesterol mean (SD) mmol/l; 5.7 (0.9) in both treatment groups. Baseline LDL-cholesterol mean (SD) mmol/l; 3.8 (0.8) in both treatment groups. The authors stated that at 3 months' follow-up pravastatin significantly improved LDL-cholesterol by -34% (95 mg/dL - no other details were reported); 11% of patients in both groups had a history of diabetes; 13% in pravastatin group and 14% in placebo group had a history of MI; 11% in both groups had a history of stroke or transient ischaemic attack.
Indirectness of population	No indirectness
Interventions	(n=2891) Intervention 1: Low intensity statin - Pravastatin 40 mg. Pravastatin 40 mg/day. Duration Mean 3.2 years. Concurrent medication/care: Nutrition and health advice (n=2913) Intervention 2: Placebo. Placebo. Duration Mean 3.2 years. Concurrent medication/care: Nutrition and health advice
Funding	Study funded by industry (Supported by an investigator grant from Bristol-Myers Squibb)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 40 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3.2 years; Group 1: 222/2891, Group 2: 254/2913; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal MI at 3.2 years; HR 0.86 (95%CI 0.72 to 1.03) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 3.2 years; Group 1: 116/2891, Group 2: 119/2913; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Non-fatal stroke at 3.2 years; HR 0.98 (95%CI 0.76 to 1.26) Reported; Risk of bias: Low; Indirectness of outcome: No

indirectness Protocol outcome 3: Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years - Actual outcome for Adults with established CVD : Rhabdomyolysis at 3.2 years; Group 1: 0/2891, Group 2: 0/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 5 years - Actual outcome for Adults with established CVD : All-cause mortality at 3.2 years; Group 1: 298/2891, Group 2: 306/2913; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : All-cause mortality at 3.2 years; HR 0.97 (95%CI 0.83 to 1.14) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: CV mortality at 5 years - Actual outcome for Adults with established CVD : Death due to coronary heart disease, stroke and vascular at 3.2 years; Group 1: 251/2891, Group 2: 293/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adverse event: Myalgia at 5 years - Actual outcome for Adults with established CVD : Myalgia at 3.2 years; Group 1: 36/2891, Group 2: 32/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Adverse event:Liver (transaminases >3 times normal level) at 5 years - Actual outcome for Adults with established CVD : Alanine and aspartate transaminases >3 the upper limit of normal at 3.2 years; Group 1: 1/2891, Group 2: 1/2913; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 8: Adverse event:New onset diabetes at 5 years - Actual outcome for Adults with established CVD : New onset diabetes at 3.2 years; Group 1: 165/2510, Group 2: 127/2513; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; LDL-cholesterol reduction at 1 year; Quality of life at 5 years

Study	**Shukla 2005[1254]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=150)
Countries and setting	Conducted in India; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographically proven CAD
Stratum	Adults with established CVD : Patients with CAD and average or below average cholesterol levels
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing coronary angioplasty and showing proven CAD were enrolled if LDL-cholesterol was <130 mg/dL and total cholesterol <200 mg/dL.
Exclusion criteria	Patients with a history of recent MI, altered liver function test, altered renal parameters, triglycerides >200 mg/dL, those already receiving lipid lowering drug therapy or alcohol intake >3 peg per day, were excluded. Patients with secondary causes of elevated cholesterol levels were also excluded (steroid therapy, hypo/hyperthyroidism, antacid containing aluminum) and so were patients with any major systemic illness.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Other: Pravastatin mean 57 years, placebo mean 55 years. Gender (M:F): 118:32. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mg/dL; 144 (26)atorvastatin, 148 (32) placebo group. Baseline LDL-cholesterol mean (SD) mg/dL; 86 (24) atorvastatin group, 84 (19) placebo group. 5% in the atorvastatin group and 4% in the placebo group had PAD. There was no information on the percentage of people with diabetes.
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg. Duration 1 year. Concurrent medication/care: All patients received dietary advice and lifestyle modification (n=75) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: All patients received dietary advice and lifestyle modification
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL cholesterol at 1 year; Group 1: mean 1.91 mmol/l (SD 0.49); n=73, Group 2: mean 2.25 mmol/l (SD 0.44); n=72; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Sola 2006[1283]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients had New York Heart Association functional class II to IV heart failure; left ventricular ejection fraction was documented by echocardiography or ventriculography during the 1 year before enrollment. Patients were classified as having non-ischaemic cardiomyopathy if they had no prior clinical history of a MI and no coronary artery stenoses >50% on cardiac catheterisation performed during year before enrolement.
Stratum	Adults with established CVD : Patients with non-ischaemic forms of cardiomyopathy
Subgroup analysis within study	Unclear
Inclusion criteria	Men and women aged 18 years or older with an NYHA functional class II to IV heart failure due to a non-ischaemic etiology; left ventricular ejection fraction =<35%; stable doses of heart failure medications for 3 months before enrollment
Exclusion criteria	Patients were excluded if they had been receiving a statin during the 6 months before enrollment, had had a prior adverse event related to statin use, had diabetes mellitus.
Recruitment/selection of patients	No details reported
Age, gender and ethnicity	Age - Mean (SD): 53.3 (SD 6.2) years atorvastatin, 54.1 (SD 6.9) placebo. Gender (M:F): 62%/38%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable /

	Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Baseline LDL-cholesterol mean (SD) mg/dL; 118 (15) atorvastatin,124 (20) placebo. Baseline total cholesterol was not reported. At 12 months LDL-cholesterol mean (SD) mg/dL; 93 (9) atorvastatin 124 (17). Patients with diabetes mellitus were excluded from this trial.
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: High intensity statin - Atorvastatin 20 mg. Atorvastatin 20 mg/day. Duration 12 months. Concurrent medication/care: At baseline: 85% were taking ACE inhibitor or ARB; 67% beta blocker; 9% aldosterone blocker; 65% diuretics (n=54) Intervention 2: Placebo. Placebo. Duration 12 months. Concurrent medication/care: At baseline: 91% were taking ACE inhibitor or ARB; 72% beta blocker; 11% aldosterone blocker; 65% diuretics
Funding	Other author(s) funded by industry (One of the study authors had been an advisory board member for Sanofi-Aventis and Bristol Myers Squibb and on the speakers bureau for Sanofi-Aventis, Bristol Myers Squibb and Takeda Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : Total mortality at 12 months; Group 1: 4/54, Group 2: 4/54; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 12 months; Group 1: mean 2.28 mmol/l (SD 0.94); n=54, Group 2: mean 2.64 mmol/l (SD 0.87); n=54; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Teo 2000**[1324]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=460)
Countries and setting	Conducted in Canada; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 3 to 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD : Patients with angiographic evidence of coronary atherosclerosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥21 years with no upper age limit, total serum cholesterol levels 4.1 - 6.2 mmol/l, HDL-cholesterol <2.2 mmol/l, triglycerides <4 mmol/l and lower than total cholesterol, angiographically detectable coronary atherosclerosis in ≥3 major coronary artery segments, left ventricular ejection fraction >35%.
Exclusion criteria	Coronary angioplasty or CABG within 6 months of recruitment, clear indications for or contraindications to study drugs, clinical instability, imminent need for intervention, other significant cardiac or systemic disease, potential non-compliance, inability to give informed consent
Recruitment/selection of patients	Patients recruited and followed up from June 1991 to July 1995 in 4 Canadian centres.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 61(9) years, placebo 61(10) years. Gender (M:F): No overall male/female ratio, simvastatin 201/29, placebo 209/21. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6.

	People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	2x2 factorial design with patients randomised to simvastatin versus placebo and enalapril versus placebo. There was a 1 month single-blind placebo run-in phase. Protocol was modified to permit identification of those with cholesterol levels persistently >5.5 mmol/l and to reallocate them to active simvastatin, in a double blind fashion.
Indirectness of population	No indirectness
Interventions	(n=230) Intervention 1: Low intensity statin - Simvastatin 10 mg. Simvastatin 10 mg/day commenced then dose automatically titrated until maximum dose of 40 mg/day or, if side effects occurred, maximally tolerated dose. Duration 3-5 years. Concurrent medication/care: Aspirin 90%, beta blockers 48%, nitrates 66%, calcium channel blockers 12% Comments: Outcomes reported as Simvastatin arm (including Simvastatin alone and Simvastatin plus Enalapril) (n=230) Intervention 2: Placebo. Placebo. Duration 3-5 years. Concurrent medication/care: Aspirin 90%, beta blockers 47%, nitrates 63%, calcium channel blockers 17% Comments: Outcomes reported as Simvastatin arm (including Simvastatin alone and Simvastatin plus Enalapril)
Funding	Study funded by industry (Merck Frosst Canada & Co)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 3-5 years; Group 1: 10/230, Group 2: 9/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Non-fatal stroke at 4-5 years; Group 1: 2/230, Group 2: 6/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3-5 years; Group 1: 13/230, Group 2: 6/230; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 5 years - Actual outcome for Adults with established CVD : Cardiac mortality at 3-5 years; Group 1: 7/230, Group 2: 4/230; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: LDL-cholesterol reduction at 1 year - Actual outcome for Adults with established CVD : LDL-cholesterol at 3-5 years; Group 1: mean 2.33 mmol/l (SD 0.49); n=230, Group 2: mean 3.43 mmol/l (SD 0.56); n=230; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Terry 2007[1325]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Angiographic evidence of coronary artery calcium ≥ 50 U
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 21 to 75 years, CAC triglycerides ≥ 50 U by CT, 600 mg/dL, 1 of the following;(1) HDL-cholesterol ≤ 50 mg/dL, LDL-cholesterol 100 to 130 mg/dL, and ≥ 2 other risk factors that modify LDL-cholesterol goal, (2) HDL-cholesterol ≤ 50 mg/dL, LDL-cholesterol 130 to 190 mg/dL, and < 2 other risk factors that modify LDL-cholesterol goal. Positive risk factors affecting goal were; age (1) ≥54 years men, ≥55 years in women, (2) parent or sibling history CAD age <55 years for men or <65 years for women, (3) current smoker, (4) hypertension, (5) HDL-cholesterol < 53 mg/dL.
Exclusion criteria	Valvular disease, diabetes, aminotransferase >20% ULN, creatine kinase >50% ULN, creatinine >1.8 mg/dL, thyroid abnormalities, women of childbearing age not practicing birth control, consumption >10 units alcohol/week, untreated hypertension, known intolerance to simvastatin.
Recruitment/selection of patients	From previous studies and mass mailing.
Age, gender and ethnicity	Age - Mean (SD): Simvastatin 66 (6) years, placebo 66 (5) years. Gender (M:F): 73:7. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear (Aged 21 to 75 years). 4. People

	with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: High intensity statin - Simvastatin 80 mg. Simvastatin 80 mg. Duration 1 year. Concurrent medication/care: Dietary advice and standard care (n=40) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Dietary advice and standard care
Funding	Other author(s) funded by industry (Merck Pharmaceuticals, Wake Forest University General Clinical Research Center North Carolina)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 80 MG versus PLACEBO Protocol outcome 1: LDL-cholesterol reduction at 1 year - Actual outcome for Adults without established CVD : LDL-cholesterol at 1 year; Group 1: mean 1.91 mmol/l (SD 0.49); n=40, Group 2: mean 3.26 mmol/l (SD 0.49); n=40; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Yamada 2007[1454]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in Japan; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: M-mode and 2-dimensional ECG performed
Stratum	Adults with established CVD : Patients with mild to moderate CHF
Subgroup analysis within study	Unclear: No subgroup analysis
Inclusion criteria	Patients with mild to moderate CHF with radionuclide left ventricular ejection fraction <40% and serum cholesterol levels from 150 to 280 mg/dL; patients had to have at least 1 hospital admission for worsening heart failure and were required to be stable on conventional therapy, including beta blockers, for at least 3 months before study entry.
Exclusion criteria	Use of lipid lowering agents during the 6 months before the start of the study, severe renal dysfunction, severe liver disease, ACS, PCI or CABG within the 6 months before study entry, and acute or chronic inflammatory diseases involving organs other than the heart.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 64 (SD 11) years. Gender (M:F): 79%/21%. Ethnicity: Asian
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men

	and women).
Extra comments	Baseline total cholesterol mean (SD) mg/dL; 198 (SD) atorvastatin, 195 (32) placebo. Baseline LDL-cholesterol mean (SD) mg/dL; 119 (27) atorvastatin, 115 (SD 37) placebo. At follow-up total cholesterol mean (SD) mg/dL; 154 (25) atorvastatin group, 192 (33) placebo. At follow-up LDL-cholesterol mean (SD) mg/dL; 76 (18) atorvastatin, 110 (35) placebo. At baseline, 22% of people had diabetes mellitus, and 53% were ischaemic.
Indirectness of population	Serious indirectness: 53% patients had ischaemic CHD
Interventions	(n=19) Intervention 1: Medium intensity statin - Atorvastatin 10 mg. Atorvastatin 10 mg/day. Duration 3 years. Concurrent medication/care: At baseline, 95% of patients were taking ACEI/ARB, 89% diuretics, 68% digoxin, and 84% beta blocker (n=19) Intervention 2: Placebo. Usual care: conventional therapy (beta blockers, ACE inhibitors, ARBs, and diuretics) were not altered for the first 6 months, thereafter the study was opened. Duration 3 years. Concurrent medication/care: At baseline, 100% of patients were taking ACE inhibitors/ARBs, 83% diuretics, 63% digoxin, and 68% beta blocker
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN 10 MG versus PLACEBO

Protocol outcome 1: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Death as a result of cardiac events at 3 years; Group 1: 0/19, Group 2: 2/19; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 1.97 mmol/l (SD 0.47); n=19, Group 2: mean 2.84 mmol/l (SD 0.91); n=19; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal MI at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5

	years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Yokoi 2005**[1463]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=373)
Countries and setting	Conducted in Japan; Setting: ARTHEROMA study. Settings were secondary care centres (cardiovascular medical centres)
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Determination of MI was made on the basis of typical chest pain and several serum enzyme values. Ischaemic stroke required both typical symptoms and an ischaemic pattern on brain computed tomography or angiogram.
Stratum	Adults with established CVD : Japanese CAD patients with slightly to moderately elevated cholesterol concentrations.
Subgroup analysis within study	Unclear
Inclusion criteria	Patients with CHD, 40-69 years of age, serum total cholesterol concentration 195-265 mg/dL, and 1 stenosis of greater than 25% in major coronary segments on visual assessment (according to the American Heart Association reporting system).
Exclusion criteria	Not reported.
Recruitment/selection of patients	Participating institutions were screened for enrolment between August 1994 and September 1997.
Age, gender and ethnicity	Age - Mean (SD): 59.3 (6.5) years. Gender (M:F): 83%/17%. Ethnicity: Japanese
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Baseline total cholesterol mean (SD) mg/dL; 226.2 (17.2) diet + pravastatin, 224.8 (17.5) diet. Baseline LDL-cholesterol mean (SD) mg/dL; 143.3 (20.6) diet + pravastatin, 142.0 (20.6) diet. Follow-up at 3 years total cholesterol mean (SD) mg/dL; 196.8 (23.0) diet + pravastatin, 223.2 (21.4) diet. Follow-up at 3 years LDL-cholesterol mean (SD) mg/dL 115.3 (20.0) diet + pravastatin, 140.7 (20.1) diet. At baseline, 19% of participants had diabetes mellitus, 14% had acute MI, 31% had prior MI, 41% had unstable angina pectoris, 12% had stable angina pectoris, and 2% had silent MI.
Indirectness of population	No indirectness
Interventions	(n=186) Intervention 1: Low intensity statin - Pravastatin 20 mg. Pravastatin 10-20 mg/day. Duration 3 years. Concurrent medication/care: Not reported (n=187) Intervention 2: Placebo. Usual care. Duration 3 years. Concurrent medication/care: Dietary counselling: low-fat and calorie reduced diet, no other drug treatments were reported
Funding	Academic or government funding (Japanese Ministry of Health and Welfare)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN 20 MG versus PLACEBO

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : Myocardial infarction at 3 years; Group 1: 2/182, Group 2: 4/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Non-fatal stroke at 5 years
- Actual outcome for Adults with established CVD : Stroke at 3 years; Group 1: 5/182, Group 2: 4/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 5 years
- Actual outcome for Adults with established CVD : All-cause mortality at 3 years; Group 1: 1/182, Group 2: 2/179; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL-cholesterol at 3 years; Group 1: mean 2.98 mmol/l (SD 0.52); n=182, Group 2: mean 3.64 mmol/l (SD 0.52); n=179: Risk of bias: Low: Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; CV mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

Study	**Zou 2003**[1494]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=197)
Countries and setting	Conducted in China; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Adults with established CVD : Patients with ACS (within 48 hours of randomisation)
Subgroup analysis within study	Not applicable
Inclusion criteria	≤48 hours of hospitalisation for a diagnosis of unstable angina or acute MI, total cholesterol ≥4.65 mmol/l or LDL-cholesterol ≥2.59 mmol/l.
Exclusion criteria	Not reported.
Age, gender and ethnicity	Age - Mean (range): Simvastatin 10 mg 61.2 (9.9) years, simvastatin 20 mg 61.3 (10.3) years. Gender (M:F): 123/74. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Baseline total cholesterol mean (mmol/l); simvastatin 10 mg 6.09, simvastatin 20 mg 4.98. Baseline LDL-cholesterol (mmol/l); simvastatin 10 mg 5.52, simvastatin 20 mg 3.51 cholesterol; 3.51. Follow-up at 1 year total cholesterol mean (mmol/l) simvastatin 10 mg 5.47, simvastatin 20 mg 4.78. Follow-up at 1 year LDL-cholesterol mmol/l: simvastatin 10

	mg 3.03, simvastatin 20 mg 2.83. Diabetes; simvastatin 10 mg 12%, simvastatin 20 mg 15%. Hypertension; simvastatin 10 mg 64%, simvastatin 20 mg 69%.
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Low intensity statin - Simvastatin 10 mg. Simvastatin 10 mg/day. Duration 1 year. Concurrent medication/care: ACE inhibitors: 26%; aspirin: 95%; beta-blockers: 90%; Calcium antagonist: 19%; nitrates: 31% (n=99) Intervention 2: Medium intensity statin - Simvastatin 20 mg. Simvastatin 20 mg/day. Duration 1 year. Concurrent medication/care: ACE inhibitors: 28%; aspirin: 97%; beta-blockers: 85%; Calcium antagonist: 23%; nitrates: 26%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN 10 MG versus SIMVASTATIN 20 MG

Protocol outcome 1: Non-fatal MI at 5 years
- Actual outcome for Adults with established CVD : MI at 1 year; Group 1: 12/98, Group 2: 7/99; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 5 years
- Actual outcome for Adults with established CVD : Coronary death at 1 year; Group 1: 2/98, Group 2: 2/99; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: LDL-cholesterol reduction at 1 year
- Actual outcome for Adults with established CVD : LDL cholesterol at 1 year; Group 1: mean 3.03 mmol/l (SD 0.53); n=98, Group 2: mean 2.83 mmol/l (SD 0.75); n=99; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 5 years; CV mortality at 5 years; Non-fatal stroke at 5 years; Adverse event: Rhabdomyolysis (CK>10 times normal) at 5 years; All-cause mortality at 5 years; Adverse event: Myalgia at 5 years; Adverse event:Liver (transaminases >3 times normal level) at 5 years; Adverse event:New onset diabetes at 5 years; Quality of life at 5 years

G.5 Adherence to statin therapy

Study	Bookstaver 2012[200]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in USA; Setting: single Army hospital
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post-intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Currently receiving statin therapy and experiencing myalgias that were generalised or present ≥2 extremities; pain had to have begun within 60 days of initiation of the drug or a dosage increase; pain present for ≥2 weeks with no other cause determined.
Exclusion criteria	Serum creatine kinase level >300 U/l; diagnosis of fibromyalgia; recent traumatic injury to the affected areas.
Age, gender and ethnicity	Age - Mean (SD): CoQ10: 31.9; Placebo: 61.8. Gender (M:F): 32/44. Ethnicity: Mostly white
Further population details	1. Black and minority ethnic groups: 2. Low socioeconomic group: 3. People age over 75 years: 4. People with a family history of CVD: 5. People with autoimmune disease: 6. People with mental illness: 7. Women:
Extra comments	Myalgia location: Calves: Simvastatin: CoQ10: 33%, Placebo: 31%. Thighs: CoQ10: 25%, Placebo: 18%. Arms: CoQ10: 13%, Placebo: 16%. Shins: CoQ10: 17%, Placebo: 11%.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Coenzyme Q10 (plus statin). CoQ10 60mg twice daily (Miller Pharmacal Group, Carol Stream, Illinois). Duration 3 months. Concurrent medication/care: Simvastatin: 22%. Pravastatin: 10%. Atorvastatin:7%. Rosuvastatin: 1%.Nonsteroidal anti-inflammatory drug: 9%. Acetaminophen: 5%. Opiate: 4%. Vitamin D: 8%. (n=36) Intervention 2: Placebo (plus statin). Matching placebo. Duration 3 months. Concurrent medication/care: Simvastatin: 22%. Pravastatin: 5%. Atorvastatin: 7%. Rosuvastatin: 2%.Nonsteroidal anti-inflammatory drug: 5%. Acetaminophen: 5%. Opiate: 4%. Vitamin D: 11%.

Funding	Funding not stated
Protocol outcomes not reported by the study	Adherence at 1 year; Adherence at 1 year; Quality of life at 1 year

Study	**Caso 2007[283]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Treated for hyperlipidemia with a statin; reporting myopatic symptoms
Exclusion criteria	Clinical evidence of hepatic, vascular, renal, or endocrine disease; coagulopathy; other serious medical conditions.
Recruitment/selection of patients	Patients recruited at cardiology clinics
Age, gender and ethnicity	Age - Mean (range): CoQ10: 58±3. Placebo: 64±2. Gender (M:F): 17/15. Ethnicity:
Further population details	1. Black and minority ethnic groups: 2. Low socioeconomic group: 3. People age over 75 years: 4. People with a family history of CVD: 5. People with autoimmune disease: 6. People with mental illness: 7. Women:
Indirectness of population	--
Interventions	(n=18) Intervention 1: Coenzyme Q10 (plus statin). Coenzyme Q10, 100 mg, (Q-Sorb softgel, Nature's Bounty, Bohemia, New York). Duration 1 month. Concurrent medication/care: Simvastatin, 11 patients (1 patient: 10 mg; 4 patients: 20 mg; 6 patients: 40 mg); Atorvastatin, 4 patients (3 patients: 10 mg; 1 patient: 20 mg); Pravastatin, 2 patients (40 mg); Lovastatin, 1 patient (40 mg). Medications with analgesic properties (nonsteroideal anti-inflammatory drugs), 5 patients. (n=14) Intervention 2: Placebo (plus statin). Vitamin E, 400 IU (softgel, Nature's Bounty). Duration 1 month. Concurrent medication/care: Simvastatin, 11 patients (3 patients: 10 mg; 3 patients: 20 mg; 3 patients: 40 mg; 2 patients: 80 mg); Atorvastatin, 3 patients (20 mg); Pravastatin, 2 patients (40 mg); Lovastatin, 1 patient (40 mg). Medications with analgesic properties (nonsteroideal anti-inflammatory drugs), 4 patients.
Funding	Academic or government funding (National Institutes of Health, Bethesda, Maryland, and the New York State Empire Clinical Research Investigator Program, Albany, New York.)

Protocol outcomes not reported by the study	Adherence at 1 year; Adherence at 1 year; Quality of life at 1 year

Study	**Young 2007[1471]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in New Zealand
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy.
Exclusion criteria	Acute MI or cerebral vascular accident within 3 months; alanine aminotransferase or aspartate aminotransferase >3 times the upper level of normal; calculated glorumeral filtration rate <45 ml/min; decompensated heart failure, warfarin treatment; antioxidant vitamin supplementation.
Age, gender and ethnicity	Age - Mean (range): CoQ10: 59±2. Placebo: 59±2. Gender (M:F): 22/22. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear
Indirectness of population	--
Interventions	(n=22) Intervention 1: Coenzyme Q10 (plus statin). Coenzyme Q-10 capsules (Q-gel; Tishcon Corporation, Salisbury, Maryland) 200 mg/day. Duration 3 months. Concurrent medication/care: Wash-out period: 2 weeks. Open-label simvastatin, titrated up from a starting dose of 10 to 20 mg/day and then to 40 mg/day at 4 weekly intervals. (n=22) Intervention 2: Placebo (plus statin). Matching placebo. Duration 3 months. Concurrent medication/care: Wash-out period: 2 weeks. Open-label simvastatin, titrated up from a starting dose of 10 to 20 mg/day and then to 40 mg/day at 4 weekly intervals.
Funding	Academic or government funding (National Heart Foundation of New Zealand)

Protocol outcomes not reported by the study	Adherence at 1 year; Adherence at 1 year; Quality of life at 1 year

G.6 Statins: predictors of adverse events

Waters 2011[1415]

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Waters et al. 2011	Prospective cohort (following on from 3 RCTs). Cox proportional hazard analysis	N=7595 TNT N=7461 IDEAL N=3803 SPARCL	TNT: 35 to 75 years, documented coronary disease, and an LDL cholesterol off therapy between 3.4 and 6.5 mmol/l (130 to 250 mg/dl), decreasing to < 3.4 mmol/l (130 mg/dl) after an 8-week run-in period on atorvastatin 10 mg/day. IDEAL: 80 years or less, had experienced a definite MI, and qualified for statin therapy according to their national guidelines at the time of recruitment. Randomised to atorvastatin 80 mg or simvastatin 20 mg/day TNT trial: subjects with new-onset type 2 diabetes mellitus (T2DM) n=659: age 60.1 (SD8.6), male 81.6%, current smokers 15%, hypertension 61.9%, fasting glucose 108.0 mg/dl (SD10.9), BMI kg/m2 30.65 (SD4.75), WBC 103/mm3 6.39 (SD1.53), SBP mm Hg 132.6 (SD17.2), DBP mm Hg 79.7 (SD9.5), total cholesterol mg/dl 178.2 (SD24.0), LDL cholesterol mg/dl 98.6 (SD17.6), HDL cholesterol mg/dl 45.2 (SD10.4), total/HDL cholesterol ratio 4.10 (SD0.91), triglycerides mg/dl 158.3 (SD78.9), use of statins during screening 63.3%, use of beta-blockers (before or at baseline) 59.6%, treatment with atorvastatin 80 mg 53.3% TNT trial: subjects without new-onset type 2 diabetes mellitus (T2DM) n=6936: age 60.7 (SD8.9), male 82.7%, current smokers 13.4%, hypertension 49.5%, fasting glucose 96.4 mg/dl (SD10.1), BMI kg/m2 27.86 (SD4.11), WBC 103/mm3 6.00 (SD1.55), SBP mm Hg	Age Fasting glucose BMI White blood count Systolic blood pressure Diastolic blood pressure Total cholesterol LDL and HDL Triglyceride Current and past smoking Hypertension Use of statins during screening Use of beta blockers Treatment with atorvastatin 80 mg or atorvastatin	TNT 4.9 years IDEAL 4.8 years SPARCL 4.9 years	New-onset diabetes defined prospectively: 2 post-baseline fasting glucose measurements ≥ 7.0 mmol/l (126 mg/dl) and at least 1 post-baseline glucose >2 mmol/l (36 mg/dl) above baseline. Patients were also identified through adverse event reporting	IDEAL funded by Pfizer Inc. Dr Chuan-Chuan Pfizer employee

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
			129.4 (SD16.2), DBP mm Hg 77.9 (SD9.3), total cholesterol mg/dl 174.2 (SD23.6), LDL cholesterol mg/dl 97.5 (SD17.3), HDL cholesterol mg/dl 48.2 (SD11.1), total/HDL cholesterol ratio 3.75 (SD0.83), triglycerides mg/dl 130.5 (SD61.7), use of statins during screening 62.3%, use of beta-blockers (before or at baseline) 53.4%, treatment with atorvastatin 80 mg 49.7% IDEAL trial: subjects with new-onset type 2 diabetes mellitus (T2DM) n=447: age 60.5 (SD8.9), male 83.2%, current smokers 21.3%, hypertension 40%, fasting glucose 107.8 mg/dl (SD10.8), BMI kg/m2 28.92 (SD4.33), WBC 103/mm3 6.81 (SD1.82), SBP, mm Hg 138.8 (SD19.6), DBP mm Hg 81.8 (SD10.2), total cholesterol mg/dl 194.9 (SD38.5), LDL cholesterol mg/dl 118.8 (SD37.7), HDL cholesterol mg/dl 42.8 (SD11.0), total/HDL cholesterol ratio 4.83 (SD1.62), triglycerides mg/dl 152.2 (SD85.7), use of statins during screening 77.6%, use of beta-blockers (before or at baseline) 79.2%, treatment with atorvastatin 80 mg 49.9% IDEAL trial: subjects without new-onset type 2 diabetes mellitus (T2DM) n=7014: age 61.6 (SD9.6), male 81.0%, current smokers 21.3%, hypertension 29.6%, fasting glucose 97.5 mg/dl (SD9.8), BMI kg/m2 26.82 (SD3.55), WBC 103/mm3 6.66 (SD1.85), SBP mm Hg 136.0 (SD20.0), DBP mm Hg 80.2 (SD10.2), total cholesterol mg/dl 196.9 (SD39.0), LDL cholesterol mg/dl 122.5 (34.7), HDL cholesterol mg/dl 46.9 (12.1), total/HDL cholesterol ratio 4.47 (SD1.40), triglycerides mg/dl 128.7 (SD64.0), use of statins during screening 75.7%,				

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
			use of beta-blockers (before or at baseline) 74.4%, treatment with atorvastatin 80 mg 49.9% SPARCL trial: subjects with new-onset type 2 diabetes mellitus (T2DM) n=281: age 62.7 (SD10.7), male 62.62%, current smokers 18.2%, hypertension 72%, fasting glucose 103.5 mg/dl (SD11.8), BMI kg/m2 29.32 (SD4.33), WBC 103/mm3 6.31 (SD1.65), SBP, mm Hg 141.8 (SD19.3), DBP mm Hg 84.1 (SD11.2), total cholesterol mg/dl 212.9 (SD27.4), LDL cholesterol mg/dl 132.2 (SD22.3), HDL cholesterol mg/dl 46.9 (SD12.5), total/HDL cholesterol ratio 4.78 (SD1.17), triglycerides mg/dl 155.6 (SD78.8), use of statins during screening 2.5%, use of beta-blockers (before or at baseline) 25.6%, treatment with atorvastatin 80 mg 59.1% SPARCL trial: subjects without new-onset type 2 diabetes mellitus (T2DM) n=3522: age 62.5 (SD11.7), male 58.8%, current smokers 19.7%, hypertension 57.2%, fasting glucose 95.2 mg/dl (SD10.2), BMI kg/m2 26.92 (SD4.33), WBC 103/mm3 6.04(SD1.74), SBP, mm Hg 137.8 (SD19.3), DBP mm Hg 81.5 (SD10.7), total cholesterol mg/dl 212.6(SD29.4), LDL cholesterol mg/dl 133.9 (SD24.3), HDL cholesterol mg/dl 51.4 (SD12.5), total/HDL cholesterol ratio 4.39 (SD1.19), triglycerides mg/dl 124.6 (SD60.4), use of statins during screening 2.4%, use of beta-blockers (before or at baseline) 17.1%, treatment with atorvastatin 80 mg 49.4%				
TNT: Age, years, 5-year increase HR 0.98 (95%CI 0.93 to 1.03) p=0.3804							

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Fasting glucose per 10-mg/dl increase 2.53 (2.34 to 2.73) p<0.0001 BMI per 3-kg/m2 increase 1.20 (1.15 to 1.25) p<0.0001 Natural log [WBC] per 0.25-1.0g (103/mm3) increase 1.16 (1.06 to 1.26) p=0.0011 SBP per 20-mm Hg increase 1.072 (0.951 to 1.210) 0.254 DBP per 10-mm Hg increase 1.024 (0.92 to 1.14) 0.655 Total/HDL cholesterol ratio per 1-U increase 1.076 (0.96 to 1.21) 0.228 Natural log [triglyceride] per 1.0-log (mg/dl) increase 1.67 (1.30 to 2.16) 0.0001 Sex, male 1.028 (0.82 to 1.28) 0.809 Current smokers 0.83 (0.623 to 1.10) 0.194 Hypertension 1.21 (1.02 to 1.43) 0.029 Use of statins during screening 1.013 (0.86 to 1.19) 0.874 Use of beta-blockers (before or at baseline) 1.022 (0.87 to 1.20) 0.789 Treatment with atorvastatin 80 mg 1.10 (0.94 to 1.29) 0.221 IDEAL trial Age, years, 5-year increase HR 0.97 (0.92 to 1.03) p=0.298 Fasting glucose per 10-mg/dl increase 2.49 (2.26 to 2.75) p<0.0001 BMI per 3-kg/m2 increase 1.28 (1.20 to 1.37) <0.0001 Natural log [WBC] per 0.25-1.0g (103/mm3) increase 1.07 (0.97 to 1.18) 0.179 SBP per 20-mm Hg increase 1.03 (0.90 to 1.17) DBP per 10-mm Hg increase 0.97 (0.86 to 1.10) 0.669 Total/HDL cholesterol ratio per 1-U increase 1.03 (0.95 to 1.12) 0.417 Natural log [triglyceride] per 1.0-log (mg/dl) increase 1.31 (0.996 to 1.73) 0.054 Sex, male 1.04 (0.80 to 1.35) 0.800 Current smokers versus never smokers 1.07 (0.77 to 1.50) 0.677 Past smokers versus never smokers 1.07 (0.82 to 1.40) 0.604 Hypertension 1.35 (1.09 to 1.67) 0.0057							

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Use of statins during screening 1.06 (0.83 to 1.35) 0.650 Use of beta-blockers (before or at baseline)1.06 (0.84 to 1.33) 0.650 Treatment with atorvastatin 80 mg 1.19 (0.99 to 1.44) 0.072							

Bruckert 2005[234]

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Bruckert et al. 2005	Prospective observational study; Multivariate logistic regression analysis	N=7294	Hyperlipidemic patients aged 18–75 years who were seen in regular outpatient visits with their general practitioners. Patients were included if they had been prescribed high-dosage statin treatment (fluvastatin 80 mg; atorvastatin 40 or 80 mg; pravastatin 40 mg; or simvastatin 40 or 80 mg) for at least 3 months prior to the study. Patients were also included if their regimen had been adjusted (statin withdrawal or dose reduction) within the last 3 months due to muscular pain. **Baseline characteristics:** **Patients without muscular symptoms** Age, years 58.4 ± 10.8 Patients aged > 65 years, N (%) 2131 (30.2%) Sex, % male 64.9% BMI, kg/m2 27.3 ± 4.4 Obese patients, N (%) 1556 (22.2%) Body fat mass, % 29.7 ± 7.9 Current smokers, N (%) 1066 (20.1%)	History of muscle pain with another LLT, unexplained cramps, history of elevated CK, history of elevated CK with LLT, history of muscular symptoms, family history of muscular symptoms, family history of muscular symptoms with LLT, hypothyroidism, duration of	1 year	Muscular symptoms defined as muscular pain, heaviness, cramps, weakness and loss of strength during exertion	Novartis Pharma SAS.

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
			Alcohol consumption, N (%) <2 drinks per day (<20 g/day) 4491 (67.3%) 2–4 drinks per day (20–40 g/day) 1706 (25.6%) >4 drinks per day (>40 g/day) 477 (7.1%) Co-medications (>2 concomitant), N (%) 4601 (65.8%) Beta-blockers 2126 (30.0%) Antidiabetic agents 1178 (16.6%) Anxiolytics 992 (14.0%) Antidepressants 568 (8.0%) Corticosteroids 48 (0.7%) **Patients with muscular symptoms** Age, years 58.7 ± 10.9 Patients aged > 65 years, N (%)262 (31.6%) Sex, % male 66.1% BMI, kg/m2 27.1 ± 4.4 Obesea patients, N (%)175 (21.3%) Body fat mass, % 28.8 ± 8.0 Current smokers, N (%)107 (16.8%) Alcohol consumption, N (%) <2 drinks per day (<20 g/day) 523 (66.7%) 2–4 drinks per day (20–40 g/day) 205 (26.2%) >4 drinks per day (>40 g/day) 56 (7.1%) Co-medications (>2 concomitant), N (%) 559 (68.8%) Beta-blockers 251 (30.2%) Antidiabetic agents 118 (14.2%)	statin treatment more than 3 months, treatment with antidepressant, background of fibromyalgia like symptoms			

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
			Anxiolytics 103 (12.4%) Antidepressants 44 (5.3%) Corticosteroids 6 (0.7%)				

Buettner 2008[245]

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Buettner 2008	Cross sectional analysis using data form National Healt and Nutrition Examination Survey(NHANES)	N=3580	Adults aged ≥40 years without a doctor's diagnosis of arthritis.	Age, sex, race, ethnicity, coronary heart disease, diabetes, cancer, systolic blood pressure, ankle brachial index, BMI, total cholesterol, smoking, health status	Prevalence study, no follow up	Myalgia	NR

Sattar 2011[1200]

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
Sattar et al. 2011	Meta-analysis of	Individual trial data extracted	Trials with data on incidence of diabetes were included in the met-analysis.	Meta-regression to	Differs by trial(range	New-onset diabetes	Trials supported by

Reference	Study type and analysis	No. of patients	Patient characteristics	Confounders included in multivariate analysis	Length of follow-up	Outcome	Source of funding
	13 trials evaluating incidence of diabetes with statin use	for review on adverse events	Trials compared statins to placebo. Refer individual data on trails from earlier review on adverse events	explore residual heterogeneity with baseline age, baseline BMI and percentage reduction in LDL cholesterol	2-6 years)		grants from pharmaceutical industry

G.7 Fibrates for prevention of CVD

Study	Anon 2000[183]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=3090)
Countries and setting	Conducted in Israel; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 6.2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age of 45 to 74 years; history of MI ≥6months but <5 years before enrollment and/or stable angina pectoris; Lipid profile of serum total cholesterol between 180 and 250 mg/dL, LDL-C ≤180mg/dL, triglycerides ≤300 mg/dL.
Exclusion criteria	Insulin-dependent diabetes mellitus, severe heart failure, unstable angina pectoris, hepatic or renal failure, known sensitivity to bezafibrate, or current use of lipid-modifying drugs.
Age, gender and ethnicity	Age - Mean (SD): 60.1±6.8 years. Gender (M:F): 2825/265. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Prior MI (%) Bezafibrate: 78.6, Placebo: 77.4. Prior angina (%) Bezafibrate: 56.6, Placebo: 57.8. Diabetes (%) Bezafibrate: 10.0, Placebo: 10.0. History of hypertension (%) Bezafibrate: 31.2, Placebo: 33.6. Stroke (%) Bezafibrate: 0.9, Placebo: 1.4. Peripheral vascular disease (%) Bezafibrate: 3.3, Placebo: 3.6.
Indirectness of population	No indirectness
Interventions	(n=1548) Intervention 1: Fibrates. Bezafibrate retard, 400 mg, once a day. Duration 6.2 years. Concurrent medication/care: Dietary advice. Colestopol 3.7%. Treatment at randomisation: Beta-blockers: 37.5%. Calcium antagonists: 50.3%. Anti-platelets: 70.7%. ACE inhibitors: 12.0%. Nitrates: 51.2%. Diuretics: 13.6%. Digitalis: 3.9%. Oral

	antidiabetic agents: 5.0% (n=1542) Intervention 2: Placebo. Matching placebo, once a day. Duration 6.2 years. Concurrent medication/care: Dietary advice. Colestopol 6.9%. Treatment at randomisation: Beta-blockers: 39.5%. Calcium antagonists: 51.8%. Antiplatelets: 69.0%. ACE inhibitors: 12.8%. Nitrates: 50.6%. Diuretics: 14.5%. Digitalis: 3.0%. Oral antidiabetic agents: 5.1%
Funding	Study funded by industry (Supported by a grant from Boehringer Mannheim GmbH, Mannheim, Germany, which is now part of F. Hoffmann-La Roche Ltd, Basel, Switzerland)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD : Non-fatal MI at 6.2 years; Group 1: 150/1548, Group 2: 172/1542; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults with established CVD : Stroke at 6.2 years; Group 1: 72/1548, Group 2: 77/1542; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 10 years - Actual outcome for Adults with established CVD : All-cause mortality at 6.2 years; Group 1: 161/1548, Group 2: 152/1542; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study	Ericsson 1996[472]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=92)
Countries and setting	Conducted in Sweden; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Survivors of a MI under 45 years of age.
Exclusion criteria	Women.
Recruitment/selection of patients	Patient screened between January 1985 and December 1988, 10 hospitals in the Stockholm County of Sweden.
Age, gender and ethnicity	Age - Other: Under 45 years. Gender (M:F): 92/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Hypertension (%): Bezafibrate 26, Placebo 16. History of angina(%): Bezafibrate 17, Placebo 16. Hypercholesterolaemia(%): Bezafibrate 15, Placebo 16. Mixed dyslipidaemia(%): Bezafibrate 81, Placebo 84. Hypertrigliceridaemia(%): Bezafibrate 4, Placebo 0. At selection, patients underwent a 3-month period of dietary intervention.
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Fibrates. Bezafibrate, 200 mg 3 times daily. Duration 5 years. Concurrent medication/care: Medication at randomisation (%): Aspirin 13; Beta-blocker 98; Calcium-channel blocker 19; Diuretics 21; Long-acting nitrates 30; ACE inhibitors 0; Other 11. (n=45) Intervention 2: Placebo. Matching placebo. Duration 5 years. Concurrent medication/care: Medication at randomisation (%): Aspirin 9; Beta-blocker 100; Calcium-channel blocker 18; Diuretics 16; Long-acting nitrates 24; ACE

	inhibitors 0; Other 4.
Funding	Study funded by industry (Grant from Boehringer Mannheim GmbH. Supplementary grants from the Karolinska Institute, the Swedish Heart-Lung Foundation, the Serafimer Foundation, and the Eirs Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD : Sudden death at 5 years; Group 1: 1/47, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Frick 1987[516] (Manttari 1987[903])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4081)
Countries and setting	Conducted in Finland; Setting: Primary care, 37 clinics.
Line of therapy	1st line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men; aged 40 to 55 years.
Exclusion criteria	Had any clinical manifestation of coronary heart disease or electrocardiographic abnormalities, congestive heart failure or any other disease that could have had an influence on the study outcome.
Recruitment/selection of patients	Employed by the Finnish Posts and Telecommunications agency, and the Finnish State Railways, and 5 industrial companies in Finland. Recruited on 1981 and 1982.
Age, gender and ethnicity	Age - Mean (range): 47.3 (40-55) years. Gender (M:F): 4081/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	Cholesterol (mmol/l) 7.47; HDL-cholesterol (mmol/l) 1.23; Non-HDL-cholesterol (mmol/l) 6.24; Systolic BP (mmHg) 141.7; Diastolic BP (mmHg) 91.3; Hypertensive 15%; Diabetics 2.7%; On beta-blocker 1.7%. Subjects with hypertension and mild non-insulin dependent diabetes were accepted.
Indirectness of population	No indirectness
Interventions	(n=2051) Intervention 1: Fibrates. Gemfibrozil 600 mg twice daily, supplied by Warner Lambert/Parker-Davis Pharmaceutical Research Division, Pontypool, UK. Duration 5 years. Concurrent medication/care: Dietary recommendations (n=2030) Intervention 2: Placebo. Placebo twice daily: Potato starch, Sucrose octa-acetate, 1.0 mg per capsule, was

	added to impart a bitter flavour and hence make it indistinguishable from the active drug. Duration 5 years. Concurrent medication/care: Dietary recommendations
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: Sudden cardiac death at 10 years - Actual outcome for Adults without established CVD : Sudden cardiac death at 5 years; Group 1: 3/2051, Group 2: 3/2030; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Myocardial infarction at 10 years - Actual outcome for Adults without established CVD : Non-fatal myocardial infarction at 5 years; Group 1: 40/2051, Group 2: 61/2030; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 10 years - Actual outcome for Adults without established CVD : All-cause mortality at 5 years; Group 1: 45/2051, Group 2: 42/2030; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study	**Frick 1997[517]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=395)
Countries and setting	Conducted in Finland; Setting: Primary care.
Line of therapy	1st line
Duration of study	Not clear: Last visit 1 year after randomisation
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients had previously undergone coronary bypass surgery. HDL cholesterol ≤1.1 mmol/L (42.5 mg/dL), LDL cholesterol ≤4.5 mmol/L (174 mg/dL), and serum triglycerides ≤4.0 mmol/L (354 mg/dL).Blood pressure ≤160/95 mm Hg; body mass index ≤30 kg/m2; left ventricular ejection fraction ≥35%; no history of diabetes and fasting serum glucose concentration <7.8 mmol/L (140 mg/dL).
Exclusion criteria	Conditions requiring therapy with calcium channel blockers, ACE inhibitors, or diuretics,smoker >20 cigarettes/wk.
Recruitment/selection of patients	Three university hospitals in Finland.
Age, gender and ethnicity	Age - Other: 59.2 years. Gender (M:F): 395/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Indirectness of population	No indirectness
Interventions	(n=198) Intervention 1: Placebo. Matching placebo. Duration 1 year. Concurrent medication/care: Previously undergone coronary artery bypass surgery (n=197) Intervention 2: Fibrates. Slow release gemfibrozil (Lopid SR) 1200 mg/day. Duration 1 year. Concurrent medication/care: Patients had previously undergone coronary artery bypass surgery
Funding	Academic or government funding (Finnish foundation for CV research, and Parke-Davis, Finnish society of Angiology)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD : All-cause mortality at 1 year; Group 1: 0/185, Group 2: 0/187; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Ginsberg 2010[553] (Bonds 2012,[198] Ginsberg 2007,[555] Ginsberg 2011,[554] Group 2007[584])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=5518)
Countries and setting	Conducted in Canada, USA; Setting: Primary care, 77 clinical sites.
Line of therapy	2nd line
Duration of study	Intervention time: Mean follow up 4.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	LDL cholesterol 1.55-4.65 mmol/L; HDL cholesterol <1.42 mmol/L for women and blacks or <1.29 mmol/L for all others; triglyceride <8.5 mmol/L if they were not receiving lipid therapy or <4.5 mmol/L if they were receiving lipid therapy.
Exclusion criteria	Non diabetics.
Recruitment/selection of patients	In the ACCORD study, all patients were randomly assigned to receive either intensive glycaemic control (targeting a glycated haemoglobin level <6.0%) or standard therapy (targeting a glycated haemoglobin level 7.0-7.9%). A subgroup of patients were enrolled in the ACCORD Lipid trial, to receive simvastatin plus either fenofibrate or placebo. Randomisation between Jan 2001 and Oct 2005. End of study visits between March and June 2009.
Age, gender and ethnicity	Age - Mean (range): 62 (40-79) years. Gender (M:F): 3824/1694. Ethnicity: White 68.4%; Black 15.1%; Hispanic 7.4%
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	All patients had type 2 diabetes and a glycated haemoglobin level ≥7.5%. Previous CV event: 36.5%; Previous congestive heart failure: 5.3%; Glycated haemoglobin (mean): 8.3±1.0; Fasting plasma glucose: 175.8±54.9 mg/dl; Total cholesterol: 175.2±37.3 mg/dl; LDL cholesterol: 100.6±30.7 mg/dl; HDL cholesterol: 38.1±7.8 mg/dl; Triglyceride (median): 162 mg/dl
Indirectness of population	No indirectness
Interventions	(n=2765) Intervention 1: Fibrates plus statin. Fenofibrate 160 mg/day at the start of the trial. Because of a rise in serum creatinine levels in some patients while receiving this dose of fenofibrate, starting in 2004 the dose was adjusted

	according to the estimated glomerular filtration rate (GFR) with the use of the abbreviated Modification of Diet in Renal Disease (MDRD). Simvastatin average dose 22.3 mg/day. Duration 4.7 years. Concurrent medication/care: Insulin: 33.2%. Metformin 61.9%. Any sulfonylurea 52.1%. Any thiazolidinedione 17.4%. Angiotensin-converting-enzyme inhibitor 53.3%. Angiotensin-receptor blocker 14.6%. Aspirin 57.3%. Beta-blocker 33.0%. Any thiazide diuretic 26.8%. Statin 59.3%. Any lipid lowering agent 64.1%. (n=2753) Intervention 2: Placebo plus statin. Matching placebo, simvastatin average dose 22.4 mg/day. Duration 4.7 years. Concurrent medication/care: Insulin: 33.3%. Metformin 62.0%. Any sulfonylurea 52.7%. Any thiazolidinedione 17.9%. Angiotensin-converting-enzyme inhibitor 54.3%. Angiotensin-receptor blocker 15.7%. Aspirin 55.3%. Beta-blocker 32.2%. Any thiazide diuretic 26.6%. Statin 60.2%. Any lipid lowering agent 64.8%
Funding	Equipment / drugs provided by industry (National Heart, Lung, and Blood Institute (NHLBI). Fenofibrate and matching placebo were donated by Abbott Lab; simvastatin was donated by Merck)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES PLUS STATIN versus PLACEBO PLUS STATIN

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome: All-cause mortality at 4.7 years; HR 0.91 (95%CI 0.75 to 1.1) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome: CV mortality at 4.7 years; HR 0.86 (95%CI 0.66 to 1.12) Reported; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome: CV mortality at 4.7 years; Group 1: 99/2765, Group 2: 114/2753; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Myocardial infarction at 10 years
- Actual outcome: Non-fatal MI at 4.7 years; Group 1: 173/2765, Group 2: 186/2753; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years
- Actual outcome: Any Stroke at 4.7 years; Group 1: 51/2765, Group 2: 48/2753; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 10 years
- Actual outcome: All-cause mortality at 4.7 years; Group 1: 203/2765, Group 2: 221/2753; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; Sudden cardiac death at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Keech 2005[746] (Anon 2007,[37] Investigators 2004[698])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=9795)
Countries and setting	Conducted in Australia, Finland, New Zealand; Setting: 63 centres; hospital clinics and community-based sources.
Line of therapy	1st line
Duration of study	Other: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria for type 2 diabetes
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Plasma total cholesterol 3.0-6.5 mmol/L plus either total-cholesterol/HDL-cholesterol ratio ≥4.0, or a plasma triglyceride concentrations 1.0-5.0 mmol/L, with no clear indication for, or treatment with, lipid-modifying therapy at study entry.
Exclusion criteria	Renal impairment (blood creatinine >130 micromol/L). Known chronic liver disease. Symptomatic gallbladder disease. Cardiovascular event within the 3 months before recruitment.
Recruitment/selection of patients	Between Feb 1998 and Nov 2000.
Age, gender and ethnicity	Age - Mean (SD): Fenofibrate: 62.2 (6.8). Placebo: 62.2 (6.9) years. Gender (M:F): 6138/3657. Ethnicity: White (93%)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=4895) Intervention 1: Fibrates. Micronised Fenofibrate 200 mg/day. Duration 5 years. Concurrent medication/care: Baseline CV medication: Any antithrombotic 32%. Angiotensin-converting enzyme inhibitor 35%. Angiotensin II receptor antagonist 6%. Beta-blocker 15%. Calcium antagonist 21%. Nitrate 5%. Diuretic 16%. Baseline blood-glucose-lowering medication: Diet alone: 26%. Metformin alone: 17%. Sulfonylurea alone 17%. Metformin+sulfonylurea 25%. Other oral agent <1%. Metformin and/or sulfonylurea+other oral agent 2%. Insulin alone 6%. Insulin+oral agent 8%. (n=4900) Intervention 2: Placebo. Matching placebo. Duration 5 years. Concurrent medication/care: Baseline CV

	medication: Any antithrombotic 32%. Angiotensin-converting enzyme inhibitor 35%. Angiotensin II receptor antagonist 5%. Beta-blocker 15%. Calcium antagonist 20%. Nitrate 6%. Diuretic 16%. Baseline blood-glucose-lowering medication: Diet alone: 26%. Metformin alone: 17%. Sulfonylurea alone 16%. Metformin+sulfonylurea 24%. Other oral agent <1%. Metformin and/or sulfonylurea+other oral agent 2%. Insulin alone 6%. Insulin+oral agent 8%.
Funding	Study funded by industry (Funded by Laboratories Fournier SA (now Abbott) and grant from the National Health and Medical Research Council (NHMRC))

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

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome: All-cause mortality at 5 years; HR 1.11 (95%CI 0.95 to 1.29) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome: CVD mortality at 5 years; HR 1.11 (95%CI 0.87 to 1.41) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Myocardial infarction at 10 years
- Actual outcome: Non-fatal myocardial infarction at 5 years; Group 1: 158/4895, Group 2: 207/4900; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years
- Actual outcome: Total stroke at 5 years; Group 1: 158/4895, Group 2: 175/4900; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: All-cause mortality at 10 years
- Actual outcome: All-cause mortality at 5 years; Group 1: 356/4895, Group 2: 323/4900; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: CV mortality at 10 years
- Actual outcome: CVD mortality at 5 years; Group 1: 140/4895, Group 2: 127/4900; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; Sudden cardiac death at 10 years; Adverse events at 10 years; Quality of life at 10 years

Study	**Meade 2002[950]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1568)
Countries and setting	Conducted in United Kingdom; Setting: 85 practices throughout the UK in the Medical Research Council's general practice research framework and in 9 hospital vascular clinics.
Line of therapy	1st line
Duration of study	Intervention time: 4.6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men with lower extremity arterial disease.
Exclusion criteria	Women.
Recruitment/selection of patients	From 1992 to 1997. Follow up ended in 2001.
Age, gender and ethnicity	Age - Mean (range): 68.2 (35-92) years. Gender (M:F): 1568/0. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Indirectness of population	No indirectness
Interventions	(n=783) Intervention 1: Fibrates. Bezafibrate 400 mg/day (as Bezalip Mono, Roche) for men with creatinine plasma concentrations <135micromol/L. Men with creatinine concentrations of 135-149 micromol/L at entry took 400 mg on alternate days. In men taking daily treatment (creatinine <135 micromol/L at entry) this was changed to alternate day treatment if concentrations rose to 155 micromol/L unless and until concentrations rose to ≥170 micromol/L, in which case men were withdrawn from trial treatment. Duration 4.6 years. Concurrent medication/care: Antiplatelet medication 65.9% (n=785) Intervention 2: Placebo. Matching placebo. Duration 4.6 years. Concurrent medication/care: Antiplatelet medication 65.9%

Funding	Equipment / drugs provided by industry (Trial tablets were supplied free of charge by Boehringer-Mannheim. Funding: Medical Research Council and British Heart Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: Stroke/Transient ischaemic attack at 10 years - Actual outcome: Fatal stroke at 4.6 years; Group 1: 13/783, Group 2: 9/785; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Non-fatal stroke at 4.6 years; Group 1: 47/783, Group 2: 40/785; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome: All-cause mortality at 4.6 years; Group 1: 204/783, Group 2: 195/785; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: CV mortality at 10 years - Actual outcome: Fatal coronary heart disease at 4.6 years; Group 1: 64/783, Group 2: 65/785; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Adverse events at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Rubins 1999[1173] (Rubins 1993,[1174] Rubins 2001[1172])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2531)
Countries and setting	Conducted in USA; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: Mean 5.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Men; age<74 years; documented history of coronary heart disease (history of MI, angina corroborated by objective evidence ischemia, coronary revascularisation, or angiographic evidence of stenosis > 50% of the luminal diameter in 1 or more major epicardial coronary arteries); absence of serious coexisting conditions; HDL cholesterol ≤ 40 mg/dL (1.0 mmol/L); LDL cholesterol ≤ 140 mg/dL (3.6 mmol/L); triglycerides ≤ 300 mg/dL (3.4 mmol/L).
Exclusion criteria	Women.
Recruitment/selection of patients	20 Veteran Affairs medical centres, between September 1991 and December 1993, final follow-up visits between May and July 1998.
Age, gender and ethnicity	Age - Mean (SD): 64 (7) years. Gender (M:F): 2531/0. Ethnicity: White (90%)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men).
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=1264) Intervention 1: Fibrates. Gemfibrozil, 1200 mg/day. From September 1991 to May 1995 patients received slow-release gemfibrozil (Lopid SR, Parke-Davis) at a dose of 1200 mg once daily. On 1 June 1995, after the manufacturer discontinued production of Lopid SR, patients received regular Gemfibrozil (Lopid, Parke-Davis) at a dose of 600 mg twice daily for the remainder of the study. Duration 5.1 years. Concurrent medication/care: Aspirin 81%. Nitrates 46%. Calcium-channel blockers 53%. ACE inhibitors 22%. Beta-blockers 43%. Any anti-anginal drug 82%

	(n=1267) Intervention 2: Placebo. Matching placebo. Duration 5.1 years. Concurrent medication/care: Aspirin 82%. Nitrates 46%. Calcium-channel blockers 52%. ACE inhibitors 20%. Beta-blockers 43%. Any anti-anginal drug 80%
Funding	Academic or government funding (Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and by a supplemental grant from Parke-Davis, a division of Earner-Lambert)

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

Protocol outcome 1: Hospitalisation at 10 years
- Actual outcome for Adults with established CVD : Hospitalisation for unstable angina and congestive heart failure at 5.1 years; Group 1: 591/1264, Group 2: 621/1267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 5.1 years; Group 1: 146/1264, Group 2: 184/1267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults with established CVD : Confirmed stroke at 5.1 years; Group 1: 58/1264, Group 2: 76/1267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD : All-cause mortality at 5.1 years; Group 1: 198/1264, Group 2: 220/1267; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Length of stay at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Steiner 2001[1294] (Steiner 1999[1295])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=418)
Countries and setting	Conducted in Canada, Finland, France, Sweden; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 years intervention + 6 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 40-65 years. Lipid entry criteria: Total cholesterol to HDL-cholesterol ratio ≥4, plus either an LDL-cholesterol concentration of 3.5-4.5 mmol/L and triglyceride concentration ≤5.2 mmol/L, or a triglyceride concentration of 1.7-5.2 mmol/L and LDL-cholesterol ≤4.5 mmol/Ll. Diabetes entry criteria: type 2 diabetes, fasting plasma glucose concentration off treatment >7.8mmol/L, or a plasma glucose concentration 2h after a 75 g oral glucose load ≥11.0mmol/L, or on treatment with glucose lowering drugs; diagnosis after age 35 years; no history of ketoacidosis; adequate glycaemic control.
Exclusion criteria	Non diabetics.
Recruitment/selection of patients	11 clinical centres.
Age, gender and ethnicity	Age - Mean (SD): Fenofibrate: 57.4 (5.7); Placebo: 56.3 (6.2) years. Gender (M:F): 305/113. Ethnicity: White (96%)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	. Men and women with type 2 diabetes, with or without previous coronary interventions. The lipid and diabetes eligibility characteristics were assessed during an 8-week dietary (American Heart Association/National Cholesterol Education Program step 1 diet) baseline period while the participant was off all lipid-lowering medications. The same diet was maintained throughout the treatment period.
Indirectness of population	No indirectness
Interventions	(n=207) Intervention 1: Fibrates. Micronised fenofibrate (200 mg/day). Duration 3 years. Concurrent medication/care:

	Each physician was allowed to adjust the glucose-lowering drug regimen to optimise control in the individual participant. (n=211) Intervention 2: Placebo. Matching placebo. Duration 3 years. Concurrent medication/care: Each physician was allowed to adjust the glucose-lowering drug regimen to optimise control in the individual participant
Funding	Study funded by industry (DAIS was supported by Laboratories Fournier SA, Daix, France)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIBRATES versus PLACEBO Protocol outcome 1: Myocardial infarction at 10 years - Actual outcome: Myocardial infarction at 3.5 years; Group 1: 9/207, Group 2: 12/211; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome: All-cause mortality at 3.5 years; Group 1: 6/207, Group 2: 9/211; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

G.8 Nicotinic acid for the prevention of CVD

Study (subsidiary papers)	**Anon 1975[6] (Sazonov 2013[1204])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3908)
Countries and setting	Conducted in USA; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: mean 74 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Standard definition of MI
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Verified evidence of 1 or more MIs (class I or II of the functional classification of the NYA), confirmed to be at least 3 months beyond their most recent MI and free from evidence of recent worsening of their coronary disease or of other major illnesses. Aged 30 between 64 years.
Exclusion criteria	Free from life-limiting disease other than CHD and diseases affecting long term follow up, no contraindication to study drug, not on anticoagulants, lipid influencing drugs or insulin at time of entry.
Recruitment/selection of patients	States randomly assigned, neither investigator nor patient informed of patient drug allocation.
Age, gender and ethnicity	Age - Mean (SD): Mean; nicotinic acid 45.0 years versus placebo 43.0 years. Gender (M:F): 3908/0. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: People aged over 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Men (Men only).
Indirectness of population	No indirectness
Interventions	(n=1119) Intervention 1: Nicotinic acid. Nicotinic acid: 3.0 g/day. Duration mean 74 months. Concurrent medication/care: Standard care (n=2789) Intervention 2: Placebo. Lactose. Duration mean 74 months. Concurrent medication/care: Not reported

Funding	Academic or government funding (National Heart and Lung Institute)

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

Protocol outcome 1: Hospitalisation at 10 years
- Actual outcome for Adults with established CVD : Ever hospitalised at 60 months; Group 1: 525/1073, Group 2: 1401/2694; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD : Impaired fasting glucose patients - Death all causes at 74 months; Risk of bias: Flawed; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Normoglycaemic patients - Death all causes at 74 months; HR 0.91 (95%CI 0.74 to 1.13) Reported; Risk of bias: Flawed; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Impaired fasting glucose patients - Death all causes at 74 months; HR 1.19 (95%CI 0.91 to 1.55) Reported; Risk of bias: ; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Type 2 diabetes patients - Death all causes at 74 months; HR 0.99 (95%CI 0.69 to 1.43) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Sudden cardiac death at 10 years
- Actual outcome for Adults with established CVD : Sudden death at 74 months; Group 1: 133/1119, Group 2: 319/2789; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD : Non-fatal MI at 74 months; Group 1: 100/1119, Group 2: 339/2789; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Normoglycaemic patients - Non-fatal MI at 74 months; HR 0.79 (95%CI 0.58 to 1.04) Reported; Risk of bias: Flawed; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Type 2 diabetes patients - Non-fatal MI at 74 months; HR 0.52 (95%CI 0.26 to 1.03) Reported; Risk of bias: Flawed; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Impaired fasting glucose patients - Non-fatal MI at 74 months; HR 0.7 (95%CI 0.46 to 1.06) Reported; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 5: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults with established CVD : Fatal or non-fatal stroke or TIA at 74 months; Group 1: 95/1119, Group 2: 311/2789; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Adverse events at 10 years - Actual outcome for Adults with established CVD : GI symptoms at 60 months; Group 1: 212/1073, Group 2: 385/2695; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Flushing at 60 months; Group 1: 987/1073, Group 2: 115/2695; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Itching of skin at 60 months; Group 1: 525/1073, Group 2: 167/2695; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Normoglycaemic patients - New onset diabetes at 74 months; HR 1.41 (95%CI 0.97 to 2.05) Reported; Risk of bias: Flawed; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD : Impaired fasting glucose patients - New onset diabetes at 74 months; HR 1.34 (95%CI 1 to 1.8) Reported; Risk of bias: ; Indirectness of outcome: No indirectness Protocol outcome 7: All-cause mortality at 10 years - Actual outcome for Adults with established CVD : Death all causes; primary end point at 74 months; Group 1: 273/1119, Group 2: 709/2789; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; CV mortality at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study	**Anon 2013[44]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=25673)
Countries and setting	Conducted in Multiple countries; Setting: Primary care.
Line of therapy	2nd line
Duration of study	Intervention time: Median 3.9 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Medical screening
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Prior MI, CV atherosclerosis, PAD, diabetes with history of CVD.
Exclusion criteria	Age <50 or >80 years, acute event <3 months, planned revascularisation within 3 months, chronic liver disease, breathlessness at rest, severe liver disease, peptic ulcer, prior reaction to statins or nicotinic acid, history poor compliance, on other lipid lowering treatment, non CVD chronic illness.
Age, gender and ethnicity	Age - Mean (SD): 64.9 (7.5) years. Gender (M:F): 21229/21195. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Indirectness of population	No indirectness
Interventions	(n=12838) Intervention 1: Nicotinic acid plus statin. ER niacin (2 g) plus laropiprant (40 mg). Duration Median 3.9 years. Concurrent medication/care: Appropriate for patient diagnosis. (n=12835) Intervention 2: Placebo plus statin. Placebo plus LDL-cholesterol lowering drug. Duration Median 3.9 years. Concurrent medication/care: Appropriate for patient diagnosis.
Funding	Other (Merck, UK Medical Research Council, British Heart Foundation, Cancer Research UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ER NIACIN PLUS LAROPIPRANT versus PLACEBO PLUS STATIN	

Protocol outcome 1: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD : Non-fatal MI at Mean 3.9 years; Group 1: 402/12838, Group 2: 431/12835; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults with established CVD : Stroke at Mean 3.9 years; Group 1: 498/12838, Group 2: 499/12835; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events at 10 years
- Actual outcome for Adults with established CVD : Rhabdomyolysis at Mean 3.9 years; Group 1: 7/12838, Group 2: 5/12835; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Any myopathy at Mean 3.9 years; Group 1: 155/12838, Group 2: 38/12835; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : Alanine transaminase > 3 x ULN at Mean 3.9 years; Group 1: 140/12838, Group 2: 67/12835; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD : GI symptoms at Mean 3.9 years; Group 1: 495/12838, Group 2: 219/12835; Risk of bias: Low; Indirectness of outcome: Serious indirectness
- Actual outcome for Adults with established CVD : Flushing at Mean 3.9 years; Group 1: 106/12838, Group 2: 14/12835; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**Investigators 2011[697] (McBride 2011[938])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=3414)
Countries and setting	Conducted in USA; Setting: Primary care.
Line of therapy	2nd line
Duration of study	Intervention time: Mean 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Documented CAD; 1 or more of the following primary criteria; 1 or more > 50% stenosis in 2 major epicardial coronary arteries. Documented cerebrovascular or carotid disease (one or more of following primary criteria satisfied; previous ischemic stroke, symptomatic carotid artery disease with >50% carotid arterial stenosis, asymptomatic carotid artery disease with >70% carotid arterial stenosis, history of carotid revascularisation, PAD; 1 or more of the following primary criteria must be satisfied): ABI <0.85 with or without symptoms of intermittent claudication, history of aorto iliac or peripheral arterial intervention (catheter-based or surgical). Atherogenic dyslipidemia: LDL-C of <180 mg/dl(4.7 mmol/l), HDL-C of <40 mg/dl(1.0 mmol/l) [men] or <50 mg/dl(1.3 mmol/l) [women] TG >150 mg/dl(1.7 mmol/l) and <400 mg/dl(4.5 mmol/l). For patients entering trial on statin + ezetimibe, the equivalent lipid criteria had to be met: the upper limit for LDL-C adjusted according to the specific statin (ezetimibe 10 mg) and statin; HDL-C of <42 mg/dl(1.1 mmol/l) [men] or <53 mg/dl(1.4 mmol/l) [women]. TG >100 mg/dl(1.1 mmol/l) and <400 mg/dl(4.5 mmol/l). Able to tolerate a minimum of 1500 mg extended-release niacin.
Exclusion criteria	CABG within 1 year of planned enrolment (run-in phase), PCI within 4 weeks of planned enrolment (run-in phase). Hospitalisation for ACS and discharge within 4 weeks of planned enrolment (run-in phase). Fasting glucose >180 mg/dl(10 mmol/l) or haemoglobin A1C >9%. For patients with diabetes, inability or refusal to use a glucometer for home monitoring of blood glucose.
Recruitment/selection of patients	Low baseline Low baseline levels of HDL-C (<40 mg/dl [1.03 mmol/l] for men; <50 mg/dl [1.29 mmol/l] for women), elevated triglyceride levels (150 to 400 mg/dl [1.69 to 4.52 mmol/l]), and LDL-C levels lower than 180 mg/dl (4.65 mmol/l) if not taking a statin at entry.
Age, gender and ethnicity	Age - Mean (SD): 64 (9) years. Gender (M:F): 2910/504. Ethnicity: 92.2% white
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of

	CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	Recruited at 92 clinical centers in the United States and Canada, aged ≥ 45 years. Stopped lipid-modifying drugs, except for statins or ezetimibe, at least 4 weeks before enrolment. 4-to-8-week open-label phase during given simvastatin (40 mg/day), plus niacin at doses that were increased weekly from 500 mg/day to 2000 mg/day
Indirectness of population	No indirectness
Interventions	(n=1718) Intervention 1: Nicotinic acid plus statin. Extended release nicotinic acid, 1500 to 2000 mg/day, simvastatin adjusted to achieve and maintain the LDL-C during study in the range of 40 to 80 mg/dl (1.03 to 2.07 mmol per/l); Ezetimibe at a dose of 10 mg per day, to achieve the target LDL-C level. Duration 3 years. Concurrent medication/care: Beta-blocker, ACE inhibitor or ARB, antiplatelet agent, received ezetimibe if needed (n=1696) Intervention 2: Placebo plus statin. Simvastatin adjusted to achieve and maintain the LDL-C during study in the range of 40 to 80 mg/dl (1.03 to 2.07 mmol per/l); Ezetimibe at a dose of 10 mg per day, to achieve the target LDL-C; Placebo had small dose (50 mg) of immediate-release niacin in each 500 mg or 1000 mg tablet. Duration 3 years. Concurrent medication/care: Beta-blocker, ACE inhibitor or ARB, antiplatelet agent, received ezetimibe if needed
Funding	Study funded by industry (National Heart, Lung and Blood Institute, and Abbott Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NICOTINIC ACID PLUS STATIN versus PLACEBO PLUS STATIN

Protocol outcome 1: Hospitalisation at 10 years
- Actual outcome: Hospitalisation for ACS only at 3 years; Group 1: 72/1718, Group 2: 82/1696; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome: All death at 3 years; Group 1: 96/1718, Group 2: 82/1696; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Myocardial infarction at 10 years
- Actual outcome: Non-fatal at 3 years; Group 1: 104/1718, Group 2: 93/1696; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years
- Actual outcome: Ischaemic stroke at 3 years; Group 1: 29/1718, Group 2: 18/1696; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Adverse events at 10 years

- Actual outcome: GI symptom at 3 years; Group 1: 12/1718, Group 2: 26/1696; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Flushing / itching at 3 years; Group 1: 104/1718, Group 2: 43/1696; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Abnormal liver function test at 3 years; Group 1: 5/1718, Group 2: 5/1696; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Increased glucose level at 3 years; Group 1: 0/0, Group 2: 0/0; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study	**Taylor 2004[1317]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=167)
Countries and setting	Conducted in USA; Setting: Primary and secondary.
Line of therapy	2nd line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Known cardiovascular disease, currently treated with statin, documented LDL-C < 130 mg/dL and HDL-C < 45 mg/dL.
Exclusion criteria	Known intolerance to nicotinic acid, history of liver disease (cirrhosis, chronic hepatitis, or abnormal liver associated enzymes (> 3 times the upper laboratory reference value).
Recruitment/selection of patients	Recruited from cardiology and general medicine services.
Age, gender and ethnicity	Age - Mean (SD): Nicotinic acid: 67 (10) years, placebo: 69 (10) years. Gender (M:F): 74/78. Ethnicity: All
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People age over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).
Extra comments	> 30 years old, 91% male.
Indirectness of population	No indirectness
Interventions	(n=87) Intervention 1: Nicotinic acid plus statin. Extended-release nicotinic acid, 500 mg for 30 days, increased to 1000 mg for duration of 12 month study, all people were receiving statin drugs on entry to the study. Duration 12 months. Concurrent medication/care: Beta-blockers, aspirin, ACE inhibitors, hypoglycaemic drugs (n=80) Intervention 2: Placebo plus statin. All people were receiving statin drugs on entry to the study. Duration 12 months. Concurrent medication/care: Beta-blockers, aspirin, ACE inhibitors, hypoglycaemic drugs

Funding	Study funded by industry (Partially funded by Kos Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTENDED RELEASE NICOTINIC ACID PLUS STATIN versus STATIN Protocol outcome 1: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD : Defined as acute coronary syndrome at 12 months; Group 1: 2/80, Group 2: 2/71; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults with established CVD : Not defined, but stated stroke only at 12 months; Group 1: 0/0, Group 2: 0/0; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 10 years - Actual outcome for Adults with established CVD : Death from all causes at 12 months; Group 1: 1/78, Group 2: 2/71; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Adverse events at 10 years; CV mortality at 10 years; Quality of life at 10 years

G.9 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

Study	**Dorr 1978-1[441]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1094)
Countries and setting	Conducted in USA; Setting: Primary care; multiple clinics.
Line of therapy	1st line
Duration of study	Intervention time: 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Primary prevention
Subgroup analysis within study	Stratified then randomised: Men
Inclusion criteria	Patients selected on the basis of serum lipids levels, consistent clinical attendance and the likelihood that they would follow a new regimen. Age ≥ 18 years; have had at least 2 of 3 biweekly fasting serum cholesterol concentrations ≥ 250 mg/dl during the 6-week period before randomisation.
Exclusion criteria	Had received steroids, other hormones (except insulin), anticoagulants, or lipid-lowering agents within the preceding 3 months; hypothyroidism or hepatic, renal or hematologic disease.
Recruitment/selection of patients	Patient enrolled at 108 clinics over a 4-year period beginning in 1969. For 6 weeks all patients took placebo, and their serum cholesterol, triglyceride, and glucose levels were determined every 2 weeks.
Age, gender and ethnicity	Age - Mean (SD): Colestipol: 50.5 (10.3) years; Placebo: 50.6 (10.5) years. Gender (M:F): 1094/0. Ethnicity: White (86%)
Further population details	
Extra comments	Hypertension: Colestipol 16.6%; Placebo 15.8%; Diabetes mellitus: Colestipol 14.8%; Placebo 12.5%; CHD: Colestipol 32.1%; Placebo 29.5%.
Indirectness of population	No indirectness
Interventions	(n=548) Intervention 1: anion exchange resin. Colestipol HCl 5 g, 3 times a day. Duration 3 years. Concurrent medication/care: None (n=546) Intervention 2: placebo. Avicel 2 g, 3 times daily. Duration 3 years. Concurrent medication/care: None

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLESTIPOL versus PLACEBO Protocol outcome 1: CV mortality at 10 years - Actual outcome: All-cardiovascular causes mortality at 3 years; Group 1: 11/548, Group 2: 24/546; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Sudden cardiac death at 10 years - Actual outcome: Sudden death unattended at 3 years; Group 1: 6/548, Group 2: 6/546; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome: Acute myocardial infarction at 3 years; Group 1: 0/548, Group 2: 8/546; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 10 years - Actual outcome: All-cause mortality at 3 years; Group 1: 17/548, Group 2: 27/546; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; Quality of life at 10 years

Study	**Dorr 1978-2**[441]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1184)
Countries and setting	Conducted in USA; Setting: Primary care, muliple clinics.
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Women
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients selected on the basis of serum lipids levels, consistent clinical attendance and likelihood of following a new regimen. Age ≥ 18 years; have had at least 2 of 3 biweekly fasting serum cholesterol concentrations ≥ 250 mg/dl during the 6-week period before randomisation.
Exclusion criteria	Women of childbearing potential; had received steroids, other hormones (except insulin), anticoagulants, or lipid-lowering agents within the preceding 3 months; hypothyroidism or hepatic, renal or hematologic disease.
Recruitment/selection of patients	Patient enrolled at 108 clinics over a 4-year period beginning in 1969. For 6 weeks all patients took placebo, and their serum cholesterol, triglyceride, and glucose levels were determined every 2 weeks.
Age, gender and ethnicity	Age - Mean (SD): Colestipol: 57.0 (10.1); Placebo: 57.1 (9.9) years. Gender (M:F): 0/1184. Ethnicity: White (76%)
Further population details	
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=601) Intervention 1: anion exchange resin. Colestipol HCl 5 g, 3 times a day. Duration 3 years. Concurrent medication/care: None (n=583) Intervention 2: placebo. Avicel 2g, 3 times daily. Duration 3 years. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLESTIPOL versus PLACEBO	

Protocol outcome 1: All-cause mortality at 10 years - Actual outcome: All-cause mortality at 3 years; Group 1: 20/601, Group 2: 21/583; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Length of stay at 10 years; Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Stroke/Transient ischaemic attack at 10 years; Adverse events at 10 years; Quality of life at 10 years

Study	**LRC-CPPT trial: Anon 1984[9]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3806)
Countries and setting	Conducted in USA; Setting: Primary care, 2 Lipid Research Clinics.
Line of therapy	1st line
Duration of study	Intervention time: 7.4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD : Men
Subgroup analysis within study	Not applicable
Inclusion criteria	Plasma cholesterol levels ≥265 mg/dL; LDL-C ≥190 mg/dL
Exclusion criteria	Triglyceride levels ≥300 mg/dL; type III hyperlipoproteinemia; history of definite or suspect MI; angina pectoris; various ECG abnormalities; congestive heart failure; hypertension or receiving antihypertensive medication; had life limiting or comorbid conditions such as cancer or non-atherosclerotic cardiovascular disease; required long-term use of certain other medications.
Recruitment/selection of patients	Screened between 1973 and 1976.
Age, gender and ethnicity	Age - Mean (range): 47.8 (35-59) years. Gender (M:F): 3806/0. Ethnicity: White
Further population details	
Extra comments	Men; aged 35-59 years; college or high school educated; caucasian; primary hypercholesterolemia (type II hyperlipoproteineamia); free of, but at high risk for CAD because of elevated LDL-C levels.
Indirectness of population	No indirectness
Interventions	(n=1906) Intervention 1: anion exchange resin. Bile acid sequestrant cholestyramine resin, 24g/day. Duration 7.4 years. Concurrent medication/care: Moderate cholesterol-lowering diet (n=1900) Intervention 2: placebo. Equivalent placebo. Duration 7.4 years. Concurrent medication/care: Moderate cholesterol-lowering diet
Funding	Academic or government funding (National Heart, Lung and Blood Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANION EXCHANGE RESIN versus PLACEBO Protocol outcome 1: Hospitalisation at 10 years - Actual outcome for Adults without established CVD : Hospitalisations with a primary diagnosis of gastro-intestinal tract disease at 7.4 years; Group 1: 314/1906, Group 2: 287/1900; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Myocardial infarction at 10 years - Actual outcome for Adults without established CVD : Definite non-fatal myocardial infarction at 7.4 years; Group 1: 130/1906, Group 2: 158/1900; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events at 10 years - Actual outcome for Adults without established CVD : Gastro-intestinal side effect at 7.4 years; Group 1: 29/1906, Group 2: 26/1900; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 10 years - Actual outcome for Adults without established CVD : All-cause mortality at 7.4 years; Group 1: 68/1906, Group 2: 71/1900; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Length of stay at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Stroke/Transient ischaemic attack at 10 years; Quality of life at 10 years

G.10 Omega-3 fatty acid compounds for the prevention of CVD

Study	**DOIT trial: Einvik 2010[456]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=563)
Countries and setting	Conducted in Norway
Line of therapy	1st line
Duration of study	Intervention time: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults without established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Hypercholesterolemia (>6.45 mmol/l).
Exclusion criteria	Total cholesterol >8 mmol/l; blood pressure >170/100 mmHg; specific disease states or practical causes thought to influence longevity, or compliance (cancer, end-stage renal failure, chronic alcoholism or travel distance >200 km).
Recruitment/selection of patients	The basis for recruitment in the DOIT was the 910 survivors from a population of 1232 healthy men with hypercholesterolemia participating in the Oslo Diet and Antismoking Study, carried out from 1972 to 1977.
Age, gender and ethnicity	Age - Range: 64-76 years. Gender (M:F): 563/0. Ethnicity: Caucasian
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: People ages less than 75 years 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: People with severe mental illness 7. Women: (Men and women).

Extra comments	Earlier CV disease: Omega 28%, Placebo 27%. Current smoking: Omega 35%, Placebo 33%. Diabetes: Omega 14%, Placebo 15%. Treated hypertension: Omega 29%, Placebo 27%. Treated hyperlipidemia: Omega 19%, Placebo 20%. The Diet and Omega-3 Intervention Trial (DOIT) on atherosclerosis was primarily conducted to investigate the progression of atherosclerosis by measurements of biochemical, functional, and structural arterial wall properties.
Indirectness of population	No indirectness
Interventions	(n=282) Intervention 1: Omega 3. Total of 2.4 g n-3 PUFA in 2 capsules twice daily (Pikasol, Lube, Denmark), of which about 49% were EPA and about 35% were DHA. The capsules also contained 3.5mg tocopherolg/g. Duration 3 years. Concurrent medication/care: Diet counseling (n=281) Intervention 2: Placebo. Corn oil capsules. 56% linoleic acid, 32% oleic acid, 10% palmitic acid (Pikasol). Duration 3 years. Concurrent medication/care: Diet counseling
Funding	Equipment / drugs provided by industry (Norwegian Cardiovascular Council, Norvegian retail company RIMI, Norvegian food company Mills DA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults without established CVD: All-cause mortality at 3 years; HR 0.57 (95%CI 0.29 to 1.1) Reported; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 10 years
- Actual outcome for Adults without established CVD: All-cause mortality at 3 years; Group 1: 14/282, Group 2: 24/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 10 years
- Actual outcome for Adults without established CVD: CV mortality at 3 years; Group 1: 7/282, Group 2: 11/281; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; Quality of life at 10 years

Study	**FORWARD trial: Macchia 2013[877]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=586)
Countries and setting	Conducted in Argentina, Italy
Line of therapy	2nd line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD: Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥21 years, with symptomatic AF who had recovered normal sinus rhythm. Patients must have had either: (1) ≥2 symptomatic episodes of documented AF in the 6 months before randomisation, with the last episode occurring within 3 to 90 days before randomisation; or (2) successful electrical or pharmacological cardioversion for persistent AF performed within 3 to 28 days before randomisation.
Exclusion criteria	Not stated.
Recruitment/selection of patients	Patients recruited from January 2008 to March 2011.
Age, gender and ethnicity	Age - Mean (SD): 66.1 (11.3) years. Gender (M:F): 9659/1665. Ethnicity: Not stated
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear (Men and women).

Extra comments	Hypertension: 91.4%. Diabetes: 12.9%. CHF: 14.1%. Stroke: 4.7%. Peripheral vascular disease: 2.4%.CAD: 11.7%
Indirectness of population	No indirectness
Interventions	(n=289) Intervention 1: Omega 3. 1 g Omega-3 PUFA (provided by SPA and Sigma-Tau, Italy), which provide 850 mg EPA and 882 mg DHA. Duration 1 year. Concurrent medication/care: Aspirin: 48.4%. Anticoagulant: 42.2%. Amiodarone: 63.3%. Any antithrombotic treatment: 77.2%. Beta-blockers: 62.5% (n=297) Intervention 2: Placebo. Olive oil. Duration 1 year. Concurrent medication/care: Aspirin: 53.2%. Anticoagulant: 42.1%. Amiodarone: 63.6%. Any antithrombotic treatment: 78.1%. Beta-blockers: 60.5%
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO Protocol outcome 1: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 1 year; Group 1: 4/289, Group 2: 5/297; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**GISSI-P trial: Marchioli 1999[906] (Tavazzi 2004[1316])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=11324)
Countries and setting	Conducted in Italy; Setting: Primary care.
Line of therapy	2nd line
Duration of study	Intervention time: 3.5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	No age limit; Recent (≤ 3 months) MI; No contraindication to the dietary supplements; Able to provide informed written consent; Had no unfavourable short-term outlook (for example, overt congestive heart failure, cancer)
Exclusion criteria	Known hypersensitivity to study treatment; conditions that in the opinion of the investigator would be associated with poor adherence to the protocol; presence of any non-cardiac co morbidity (for example, cancer) unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within 1 month; planned cardiac surgery, expected to be performed within 3 months after randomisation; significant liver disease; pregnant or lactating women or women of childbearing potential who are not protected from pregnancy by an accepted method of contraception.
Age, gender and ethnicity	Age - Mean (SD): 59.4 (10.6) years. Gender (M:F): 9659/1165. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female

Extra comments	Omega Group (n = 2836), Control group (n = 2828) n (%) Arterial hypertension: 1019 (36.0), 967 (34.2); Diabetes mellitus: 405 (14.2), 426 (15.0); Previous MI: 326 (11.6), 333 (11.9). Omega Group (n = 2836), Control group (n = 2828) n (%) Arterial hypertension: 1019 (36.0), 967 (34.2); Diabetes mellitus: 405 (14.2), 426 (15.0); Previous MI: 326 (11.6), 333 (11.9)
Indirectness of population	Serious indirectness: Patients were asked to adhere to recommended preventive treatments: aspirin, B-blockers, inhibitors of angiotensin-converting enzyme (statins were not supported by definitive data on efficacy when the trial was started)
Interventions	(n=5666) Intervention 1: Omega 3. n = 2836: n-3 PUFA (850-882 mg eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) at a ratio of EPA/DHA 1:2), gelatine capsule, n = 2830: n-e PUFA + vit E. Duration 3.5. Concurrent medication/care: Angiotensin-converting-enzyme inhibitors, Baseline: 2650 (46.8%), 42 months: 1614 (28.5%), B-blocker, Baseline: 2487 (50.2%), 42 months: 1571 (27.7%), Cholesterol-lowering drugs, Baseline: 259 (4.6%), 42 months: 2016 (35.6%) (n=5658) Intervention 2: Placebo. n=2830: 300 mg vitamin E, syntetic α-tocopherol, capsule, n=2828: Placebo. Duration 3.5 years. Concurrent medication/care: Angiotensin-converting-enzyme inhibitors, Baseline: 2630 (46.5%), 42 months: 1528 (27.0%), B-blocker, Baseline: 2499 (44.1%), 42 months: 1528 (27.0%), Cholesterol-lowering drugs, Baseline: 275 (4.9%), 42 months: 1903 (33.6%)
Funding	Study funded by industry (Grants from Bristol-Myers Squibb, Pharmacia-Upjohn, Societa' Prodotti Antibiotici, Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All-cause mortality at 3.5 years; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults with established CVD: All-cause mortality at 3.5 years; Group 1: 472/5666, Group 2: 545/5658; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome for Adults with established CVD: CV mortality (cardiac, coronary and sudden death) at 3.5 years; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adults with established CVD: CV mortality (cardiac, coronary and sudden death) at 3.5 years; Group 1: 291/5666, Group 2: 348/5658; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV events (MI, Stroke) at 10 years
- Actual outcome for Adults with established CVD: Non-fatal CV events at 3.5 years; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years
- Actual outcome for Adults with established CVD: Fatal and Non-fatal stroke at 3.5 years; Group 1: 98/5666, Group 2: 80/5658; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Sudden cardiac death at 10 years
- Actual outcome for Adults with established CVD: Sudden death at 3.5 years; Group 1: 122/5666, Group 2: 164/5658; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; Myocardial infarction at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**JELIS trial: Yokoyama 2007[1466] (Yokoyama 2003[1465])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=18645)
Countries and setting	Conducted in Japan; Setting: Primary care. Population exclusively Japanese. In Japan, death from coronary artery disease is rare (22-26 per 100,000 person-years) and average dietary intake of fish is about 5 times higher than other countries.
Line of therapy	2nd line
Duration of study	Intervention time: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Primary and secondary prevention of CVD.
Inclusion criteria	Total cholesterol of 6.5 mmol/L or greater (LDL-cholesterol of 4.4 mmol/l or greater).
Exclusion criteria	Acute MI within the past 6 months; unstable angina pectoris; history or complication of serious heart disease (such as severe arrhythmia, heart failure, cardiomyopaty, valvular disease, or congenital disease); cardiovascular reconstruction within the past 6 months; cerebrovascular disorder within the past 6 months; complications or serious hepatic or renal disease; Malignant disease; Uncontrollable diabetes; Hyperlipidaemia due to other disorder; Hyperlipidaemia caused by drugs such as steroid hormones; haemorrhage; haemorrhagic diathesis; hypersensitivity to the study drug formulation; patients' intention to undergo surgery; judgement by the physician in charge that a patient was inappropriate for the study.
Recruitment/selection of patients	Between Nov 1996 and Nov 1999. Study patients recruited by local physicians participating in the study, with the help of regional organising committees.
Age, gender and ethnicity	Age - Mean (SD): Omega: 61 (8); Placebo: 61 (9) years. Gender (M:F): 5859/12786. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: All socioeconomic groups 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Extra comments	MI[n (%)]: Omega: 584 (6), Placebo: 502 (5); Diabetes [n (%)]: Omega: 1516 (16), Placebo: 1524 (16); Hypertension [n (%)]: Omega: 3329 (36), Placebo: 3282 (35); Total cholesterol (mmol/l): Omega: 7.11 (0.67), Placebo: 7.11 (0.68). MI [n (%)]: Omega: 584 (6), Placebo: 502 (5); Diabetes [n (%)]: Omega: 1516 (16), Placebo: 1524 (16); Hypertension [n (%)]: Omega: 3329 (36), Placebo: 3282 (35); Total cholesterol (mmol/l): Omega: 7.11 (0.67), Placebo: 7.11 (0.68). MI [n (%)]: Omega: 584 (6), Placebo: 502 (5); Diabetes [n (%)]: Omega: 1516 (16), Placebo: 1524 (16); Hypertension [n (%)]: Omega: 3329 (36), Placebo: 3282 (35); Total cholesterol (mmol/l): Omega: 7.11 (0.67), Placebo: 7.11 (0.68)
Indirectness of population	No indirectness
Interventions	(n=9326) Intervention 1: Omega 3 plus Statins - Statins+Omega. EPA 1800 mg/day (600 mg 3 times a day after meals). Capsules containing 300 mg of highly purified (>98%) EPA ethyl ester (Mochida Pharmaceutical, Tokyo, Japan). Duration 4.6 years. Concurrent medication/care: All patients received either 10 mg pravastatin or 5 mg simvastatin once daily. (n=9319) Intervention 2: Placebo plus Statins - Statins+Placebo. No treatment. Duration 4.6 years. Concurrent medication/care: All patients received either 10 mg pravastatin or 5 mg simvastatin once daily.
Funding	Study funded by industry (Grants from Mochida Pharmaceutical Co Ltd, Tokyo, Japan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STATINS+OMEGA versus STATINS+PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome: All-cause mortality at 4.6 years; HR 1.09 (95%CI 0.92 to 1.28) Reported; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: All-cause mortality at 4.6 years; Group 1: 286/9326, Group 2: 265/9319; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome: Sudden cardiac death at 4.6 years; HR 1.06 (95%CI 0.55 to 2.07) Reported; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Coronary death at 4.6 years; HR 0.94 (95%CI 0.57 to 1.56) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: CV events (MI, Stroke) at 10 years - Actual outcome: Unstable angina at 4.6 years; HR 0.76 (95%CI 0.62 to 0.95) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years - Actual outcome: Stroke at 4.6 years; Group 1: 166/9326, Group 2: 162/9319; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Sudden cardiac death at 10 years - Actual outcome for Adults without established CVD: Sudden cardiac death (Primary prevention) at 4.6 years; Group 1: 5/7503, Group 2: 4/7478; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD: Sudden cardiac death (Secondary prevention) at 4.6 years; Group 1: 13/1823, Group 2: 13/1841; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Myocardial infarction at 10 years - Actual outcome: Fatal and non-fatal MI at 4.6 years; Group 1: 71/9326, Group 2: 93/9319; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD: Fatal and non-fatal MI (Primary prevention) at 4.6 years; Group 1: 40/7503, Group 2: 51/7478; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD: Fatal and non-fatal MI (Secondary prevention) at 4.6 years; Group 1: 31/1823, Group 2: 42/1841; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 7: CV mortality at 10 years - Actual outcome: Coronary death at 4.6 years; Group 1: 29/9326, Group 2: 31/9319; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults without established CVD: Coronary death (Primary prevention) at 4.6 years; Group 1: 10/7503, Group 2: 11/7478; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD: Coronary death (Secondary prevention) at 4.6 years; Group 1: 18/1823, Group 2: 21/1841; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; Quality of life at 10 years

Study	**Nilsen 2001**[1027]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=300)
Countries and setting	Conducted in Finland; Setting: Primary care.
Line of therapy	1st line
Duration of study	Not clear: 1.5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria
Stratum	Adults with established CVD: Patients with acute MI
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute MI, age >18 years, discontinuation of fish supplements, informed consent.
Exclusion criteria	Assumed noncompliance, expected survival <2 years, GI bleeding, thrombocytopenia, liver insufficiency.
Recruitment/selection of patients	Patients recruited at 1 hospital center (Central Hospital in Rogaland, Stavanger, Norway) from September 1995 until December 1996.
Age, gender and ethnicity	Age - Range: Omega 3: 28.9-29.3 years; Placebo: 29.3-87.7 years. Gender (M:F): 238/62. Ethnicity: Not stated (assumed white)
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female

Extra comments	Angina pectoris: Omega 3: 32.9%; Placebo: 38.0%. Heart failure: Omega 3: 10.0%; Placebo: 7.4%. Previous MI: Omega 3: 21.3%; Placebo: 25.3%. Revascularisation: Omega 3: 8.0%; Placebo: 10.0%. Hypertension: Omega 3: 28.6%; Placebo: 22.8%. Diabetes: Omega 3: 12.0%; Placebo: 8.7%. Angina pectoris: Omega 3: 32.9%; Placebo: 38.0%. Heart failure: Omega 3: 10.0%; Placebo: 7.4%. Previous MI: Omega 3: 21.3%; Placebo: 25.3%. Revascularisation: Omega 3: 8.0%; Placebo: 10.0%. Hypertension: Omega 3: 28.6%; Placebo: 22.8%. Diabetes: Omega 3: 12.0%; Placebo: 8.7%.
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Omega 3. 2 gelatin capsules of Omacor-R (Pronova AS, Oslo) twice a day. Each capsule contained 850–882 mg EPA and DHA in the average ratio of EPA to DHA of 1:2 Tocopherol (4 mg) was added to all capsules, (4g/day). Duration 1.5 years. Concurrent medication/care: First 24h. Beta-blocker: 52.7%. ACE inhibitors: 14.1%. Diuretics: 26.7%. Aspirin: 91.3%. Statin: 42.2% (n=150) Intervention 2: Placebo. 2 gelatin capsules of corn oil twice a day (4g/day). Duration 1.5 years. Concurrent medication/care: First 24h. Beta-blocker: 51.3%. ACE inhibitors: 20.0%. Diuretics: 24.0%. Aspirin: 88.0%. Statin: 45.0%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All-cause mortality at 1.5 years ; Group 1: 11/150, Group 2: 11/150; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD: Recurrent MI at 1.5 years; Group 1: 21/150, Group 2: 15/150; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV mortality at 10 years
- Actual outcome for Adults with established CVD: Cardiac death at 1.5 years; Group 1: 8/150, Group 2: 8/150; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**OMEGA trial: Rauch 2010[1138] (Rauch 2006[1139])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=3084)
Countries and setting	Conducted in Germany; Setting: Primary care
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years, admitted to hospital for acute STEMI or non-STEMI.
Exclusion criteria	Pre-menopausal women, who were pregnant, nursing or not practicing birth control, and women who do not agree pregnancy test before participating in the study; known hypersensitivity to any component of the study drugs; patients with haemorrhagic diathesis; patients not willing to discontinue other medication containing fish oils; known or suspected non-compliance; legal incapacity and/or other circumstances rendering the patient unable to understand the study; refusal or withdrawal of the informed consent; history of drug or alcohol abuse within 6 months; any investigational therapy within 1 month of signing the informed consent; any other clinical condition which would not allow safe completion of the protocol and administration of the study drugs.
Recruitment/selection of patients	3 to 14 days after acute myocardial infarction (STEMI or non-STEMI).
Age, gender and ethnicity	Age - Median (range): 64.0 years. Gender (M:F): 1445/1396. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history

	of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Extra comments	. Diabetes mellitus, % (n) Omega: 27.6 (532) Placebo: 26.4 (500).
Indirectness of population	No indirectness
Interventions	(n=1925) Intervention 1: Omega 3. 1 g omega-3 acid ethyl esters-90 (460 mg eicosapentaenoic, 380 mg docosahexaeonic acid), soft gelatine capsule. Duration 1 year. Concurrent medication/care: B-blockers, % (n) 93.9 (1796), Angiotensin-converting enzyme inhibitors, % (n) 82.9 (1586), Statin, % (n) 94.6 (1810), Acetylsalicylic acid, % (n) 95.6 (1828), Clopidogrel, % (n) 88.0 (1683), Calcium channel blockers, % (n) 8.1 (154) (n=1893) Intervention 2: Placebo. 1 g olive oil, soft gelatine capsule. Duration 1 year. Concurrent medication/care: B-blockers, % (n) 94.3 (1778), Angiotensin-converting enzyme inhibitors, % (n) 83.7 (1578), Statin, % (n) 93.8 (1768)
Funding	Study funded by industry (Trommsdorff GmbH &Co. KG Arzneimittel, Alsdorf, Germany, and Pronova Biopharma, Lysaker, Norway)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All-cause mortality at 1 year; HR 1.24 (95%CI 0.91 to 1.7) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome for Adults with established CVD: Sudden cardiac death at 1 year; HR 1.05 (95%CI 0.63 to 1.77) Calculated – from logrank P-value; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: CV events (MI, Stroke) at 10 years
- Actual outcome for Adults with established CVD: MACCE at 1 year; Group 1: 182/1752, Group 2: 149/1701; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Sudden cardiac death at 10 years
- Actual outcome for Adults with established CVD: Sudden cardiac death at 1 year; Group 1: 28/1919, Group 2: 29/1885; Risk of bias: Low; Indirectness of outcome: No

indirectness Protocol outcome 5: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 1 year; Group 1: 88/1919, Group 2: 70/1885; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; Adverse events at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Myocardial infarction at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**ORIGIN trial: Origin trial 2008[1058] (Bosch 2012[202])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=12,536)
Countries and setting	Conducted in Multiple countries; Setting: Primary care. International (40 countries) multicentre.
Line of therapy	2nd line
Duration of study	Intervention time: 6.2 years (median)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with type 2 diabetes: Type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥50 years. Either IFG, IGT, or newly detected diabetes; or established type 2 diabetes on stable therapy with 0 or 1 oral agent for ≥3 months. Confirmed evidence of at least 1 of (a) prior MI, or stroke, or revascularisation; (b) angina with documented ischemia; (c) a first morning urinary albumin/creatinine ration >30 microgram/mg; (d) evidence of left ventricular hypertrophy; (e) ≥50% stenosis of a coronary, carotid, or lower extremity artery documented angiographically; or (f) ankle/brachial index <0.9.
Exclusion criteria	Use, indication of, or intolerance to insulin or PUFA; unwillingness to stop thiazolidine-diones (TZDs) if allocated to glargine; a glycated haemoglobin ≥150% ULN; coronary artery bypass grafting within 4 years of screening with no intervening CV events; or heart failure.
Recruitment/selection of patients	Randomisation ended December 2005.
Age, gender and ethnicity	Age - Mean (SD): 63.6 (7.84) years. Gender (M:F): 65%/35%. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history

	of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female
Extra comments	Hypertension: 85.8%. Dyslipidemia: 69.5%. Known albuminuria: 15.4%. With previous CVD: 66.4%. With previous revascularisation: 32.8%. With neuropathy: 9.6%. 2-by-2 factorial design; patients randomly assigned to receive a 1g capsule containing at least 900 mg (90% or more) of ethyl esters of n–3 fatty acids as compared with placebo and of insulin glargine as compared with standard care.
Indirectness of population	No indirectness
Interventions	(n=6281) Intervention 1: Omega 3. 1 g capsule containing at least 900 mg (90% or more) of ethyl esters of n–3 fatty acids (containing 465 mg of eicosapentaenoic acid [EPA] and 375 mg of docosahexaenoic acid [DHA]). (Omacor, Pronova BioPharma Norge). Duration 6.2 years. Concurrent medication/care: ACE inhibitor or ARB: 68.8%. Thiazide diuretics: 18.8%. Aspirin or other antiplatelet agent: 69.6%. Anticoagulant: 7.0%. Beta-blocker: 52.8%. Calcium-channel blocker: 27.2%. Statin: 53.0%. (n=6255) Intervention 2: Placebo. Approx 1 g of olive oil. Duration 6.2 years. Concurrent medication/care: ACE inhibitor or ARB: 68.7%. Thiazide diuretics: 19.0%. Aspirin or other antiplatelet agent: 68.6%. Anticoagulant: 6.9%. Beta-blocker: 52.5%. Calcium-channel blocker: 28.0%. Statin: 54.5%.
Funding	Equipment / drugs provided by industry (Supported by Sanofi, with study drugs provided by Pronova BioPharma Norge)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with type 2 diabetes: All-cause mortality at 6.2 years; HR 0.98 (95%CI 0.89 to 1.07) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: CV mortality at 10 years
- Actual outcome for Adults with type 2 diabetes: CV mortality at 6.2 years; HR 0.98 (95%CI 0.87 to 1.1) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Stroke/Transient ischaemic attack at 10 years

- Actual outcome for Adults with type 2 diabetes: Fatal and non-fatal stroke at 6.2 years; Group 1: 314/6281, Group 2: 336/6255; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: All-cause mortality at 10 years - Actual outcome for Adults with type 2 diabetes: All-cause mortality at 6.2 years; Group 1: 951/6281, Group 2: 964/6255; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Myocardial infarction at 10 years - Actual outcome for Adults with type 2 diabetes: Fatal and non-fatal MI at 6.2 years; Group 1: 344/6281, Group 2: 316/6255; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: CV mortality at 10 years - Actual outcome for Adults with type 2 diabetes: CV mortality at 6.2 years; Group 1: 574/6281, Group 2: 581/6255; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; CV events (MI, Stroke) at 10 years; Adverse events at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; Quality of life at 10 years

Study	**Singh 1997[1270]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=240)
Countries and setting	Conducted in India; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Only those patients judged likely to have suffered acute MI with onset of symptoms in the preceding 24 hours were eligible for the study.
Exclusion criteria	There were no exclusion criteria; however, those patients who died immediately after admission, patients unable or refusing to give verbal consent, and patients who were admitted later than 24 hours after the onset of symptoms were excluded.
Recruitment/selection of patients	Medical Hospital and Research Centre, Moradabad, which is both a primary and secondary care center.
Age, gender and ethnicity	Age - Mean (SD): Omega 3: 48.5 (6.5). Placebo: 49.2 (7.2) years. Gender (M:F): Not reported. Ethnicity: Not stated (assumed South Asian)
Further population details	1. Black and minority ethnic groups: Asian 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female

Indirectness of population	No indirectness
Interventions	(n=122) Intervention 1: Omega 3. The test drug fish oil is marketed under the trade name Maxepa by Universal Generics Private Limited (Bombay, India). Each capsule contains 180 mg EPA and 120 mg DHA. 2 capsule 3 times daily (1.08 g/day of EPA and 0.72 g/day of DHA). Duration 1 year. Concurrent medication/care: Atenolol (100-150 mg/day): 29.4%. Diltiazem (60180 mg/day): 24.6%. Nitrates (20-60 mg/day): 75.4%. Aspirin (100-150 mg/day): 90.1% (n=118) Intervention 2: Placebo. The placebo capsules contained 100 mg/day of aluminum hydroxide. Duration 1 year. Concurrent medication/care: Atenolol (100-150 mg/day): 28.7%. Diltiazem (60180 mg/day): 27.0%. Nitrates (20-60 mg/day): 93.2%. Aspirin (100-150 mg/day): 98.3%
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: Adverse events at 10 years
- Actual outcome for Adults with established CVD: Adverse events (belching and nausea) at 1 year; Group 1: 14/122, Group 2: 0/118; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Sudden cardiac death at 10 years
- Actual outcome for Adults with established CVD: Sudden cardiac death at 1 year; Group 1: 2/122, Group 2: 8/118; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Myocardial infarction at 10 years
- Actual outcome for Adults with established CVD: Non-fatal MI at 1 year; Group 1: 16/122, Group 2: 30/118; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: CV mortality at 10 years
- Actual outcome for Adults with established CVD: Total cardiac death at 1 year; Group 1: 14/122, Group 2: 26/118; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years;

	Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; All-cause mortality at 10 years; Quality of life at 10 years

Study (subsidiary papers)	**SU.FOL.OM3 trial: Galan 2011[532] (Galan 2003,[531] Galan 2008[533])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=2501)
Countries and setting	Conducted in France; Setting: Multicentre
Line of therapy	1st line
Duration of study	Intervention time: Median 4.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 45-80 years; had an acute coronary or cerebral ischemic event within the 12 months before randomisation.
Exclusion criteria	Age<45 yr or >80yr; ill defined diagnosis of cardiovascular disease; inability or unwillingness to comply with study treatment; disease or treatment that might interfere with metabolism of homocysteine or omega 3 fatty acids (in particular methotrexate for treating cancer or rheumatoid arthritis
Recruitment/selection of patients	Participants with a history of CV disease were recruited via a network of 417 cardiologists, neurologists, and other physicians in 257 centres throughout France.
Age, gender and ethnicity	Age - Range: 53.9-58.9 years. Gender (M:F): 1987/514. Ethnicity: Not reported
Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Male+female

Extra comments	Omega Group (n = 633) Control group (n = 626) n (%) Beta-blockers 431 (68.1) 428 (68.4); calcium channel blockers 103 (16.3) 86 (13.7); lipid lowering agent 544 (85.9) 544 (86.9); aspirin or antiplatelet agents 595 (94.0) 588 (93.9); ACE inhibitors 331 (52.3) 342 (54.6). Omega Group (n = 633) Control group (n = 626) n (%) Beta-blockers 431 (68.1) 428 (68.4); calcium channel blockers 103 (16.3) 86 (13.7); lipid lowering agent 544 (85.9) 544 (86.9); aspirin or antiplatelet agents 595 (94.0) 588 (93.9); ACE inhibitors 331 (52.3) 342 (54.6)
Indirectness of population	No indirectness
Interventions	(n=1248) Intervention 1: Placebo. n=626: Placebo, gelatine capsule, n=622: 5-methyltetrahydrofolate (560 microgrammes), Vitamin B-6 (3mg) and B-12 (20 microgrammes). Duration 5 years. Concurrent medication/care: n (%): Beta-blockers: 428 (68.4); calcium and channel blockers: 86 (13.7); lipid lowering agent: 544 (86.9); aspirin or antiplatelet agents: 588 (93.9); ACE inhibitors: 342 (54.6) (n=1253) Intervention 2: Omega 3. n=633: omega-3 polyunsaturated fatty acid (600 mg eicosapentanoic acid and docosahexaenoic acid at a ratio of 2:1), gelatine capsule, n=620: B vitamins + omega 3 fatty acids. Duration 5 years. Concurrent medication/care: Omega Group (n = 633) Control group (n = 626) n (%) Beta-blockers: 431 (68.1); calcium and channel blockers: 103 (16.3); lipid lowering agent: 544 (85.9); aspirin or antiplatelet agents: 595 (94.0); ACE inhibitors: 331 (52.3)
Funding	Academic or government funding (French Ministry of Research, Ministry of Health, Sodexo, Candia, Unilever, Danone, Roche Laboratory, Merck EPROVA GS, and Pierre Fabre Laboratory)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO

Protocol outcome 1: All-cause mortality at 10 years
- Actual outcome for Adults with established CVD: All-cause mortality at 5 years; HR 1.03 (95%CI 0.72 to 1.48) Reported; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: CV events (MI, Stroke) at 10 years
- Actual outcome for Adults with established CVD: Major cardiovascular events: Non-fatal myocardial infarction, ischaemic stroke, or death from CV disease (incl fatal myocardial infarction, stroke, sudden death, aortic dissection, cardiac failure, or other fatal event defined by the medical committee as having CV cause) at 5 years; HR 1.08 (95%CI 0.79 to 1.47) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults with established CVD: Non-fatal myocardial infarction at 5 years; HR 1.15 (95%CI 0.69 to 1.9) Reported; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events at 10 years - Actual outcome for Adults with established CVD: Side effects (gastrointestinal disturbances, nausea and cutaneous reaction) at 5 years; Group 1: 16/1253, Group 2: 10/1248; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Stroke/Transient ischaemic attack at 10 years - Actual outcome for Adults with established CVD: Stroke at 5 years; HR 1.04 (95%CI 0.62 to 1.75) Reported; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults with established CVD: Stroke at 5 years; Group 1: 29/1253, Group 2: 28/1248; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 5 years; Group 1: 58/1253, Group 2: 59/1248; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Non-fatal myocardial infarction at 5 years; Group 1: 32/1253, Group 2: 28/1248; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; CV mortality at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years

Study	**Von schacky 1999[1386]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=223)
Countries and setting	Conducted in Germany; Setting: Primary care.
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with established CVD: Patients with proven CAD
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	1) stenosis greater than 20% in at least 1 vessel and 2) revascularisation (percutaneous transluminal coronary angioplasty [PTCA] or coronary bypass surgery) planned or performed in the previous 6 months in no more than 1 vessel
Exclusion criteria	History of cardiac transplantation, age younger than 18 years or older than 75 years, haemodynamically relevant left main stenosis or proximal stenosis in all 3 main vessels, biplane left ventricular ejection fraction less than 35%, ventricular tachycardias ($3 QRS complexes), haemodynamically relevant cardiac valve disease, a prognosis severely limited by noncardiac disease, bleeding tendency (for example, due to thrombocytopenia or anticoagulation), diabetes, or other evidence of increased risk. Patients were not asked to participate if they were participating in another study, had psychiatric disease, had a history of noncompliance, lived too far away, had an initial coronary angiogram of poor quality, or had a history of allergic reaction to contrast material.
Recruitment/selection of patients	Patients hospitalised for diagnostic coronary angiography between 1 Sept 1992 and 19 May 1994.
Age, gender and ethnicity	Age - Mean (range): Omega 3: 57.8±9.7; Placebo: 58.9±8.1 years. Gender (M:F): 179/44. Ethnicity: Not reported

Further population details	1. Black and minority ethnic groups: Not applicable / Not stated / Unclear 2. Low socioeconomic group: Not applicable / Not stated / Unclear 3. People aged over 75 years: Not applicable / Not stated / Unclear 4. People with a family history of CVD: Not applicable / Not stated / Unclear 5. People with autoimmune disease: Not applicable / Not stated / Unclear 6. People with severe mental illness: Not applicable / Not stated / Unclear 7. Women: Not applicable / Not stated / Unclear
Extra comments	History of elevated blood lipid levels: Omega 3: 61.3%; Placebo: 62.5%. Mean cholesterol levels±SD, mmol/l: Omega 3: 6.30±1.12; Placebo: 6.10±1.13. Previous MI: Omega 3: 52.3%; Placebo: 50.9%. History of elevated blood lipid levels: Omega 3: 61.3%; Placebo: 62.5%. Mean cholesterol levels±SD, mmol/L: Omega 3: 6.30±1.12; Placebo: 6.10±1.13. Previous MI: Omega 3: 52.3%; Placebo: 50.9%.
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Omega 3. Each capsule contained each contained 1 g of a fatty acid mixture. The fatty acid mixture in the fish oil capsules was 0.9% C16:0, 6.0% C18:0, 4.5% C18:1v-9, 0% C18:2v-6, 0.6% C18:3v-3, 1.4% C20:4v-6, 35.4% C20:5v-3, 9.7% C22:5v-3, 21.5% C22:6v-3, and 20.0% other compounds. The peroxide values were 0.5 in the placebo capsules and 0.6 in the fish oil capsules. All capsules contained 4 mg of tocopherol-a as an antioxidant. Duration 2 years. Concurrent medication/care: Platelet inhibitors: 91.9%; beta-blockers: 71.2%; Long-term nitrate therapy: 46.8%; Nitrates only on demand: 8.1%; Lipid-lowering agents: 25.2% (n=112) Intervention 2: Placebo. Placebo. Duration 2 years. Concurrent medication/care: Platelet inhibitors: 91.1%; beta-blockers: 71.4%; Long-term nitrate therapy: 42.0%; Nitrates only on demand: 10.7%; Lipid-lowering agents: 25.9%
Funding	Study funded by industry (Grant Support: In part by the Bundesministerium fu¨r Forschung und Technologie, Germany, through Gesellschaft fu¨r Strahlenforschung (GSF, 07ERG03) and Deutsche Forschungsanstalt fu¨r Luft- und Raumfahrt (DLR, 01 EA 9501/7); Wilhelm Sander Stiftung (93.032); Fundacion Federico; and the Deutsche For schungsgemeinschaft provided the capsules and funds for monitoring)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OMEGA 3 versus PLACEBO Protocol outcome 1: Adverse events at 10 years - Actual outcome for Adults with established CVD: Adverse events (mild gastrointestinal discomfort) at 2 years: Group 1: 4/111, Group 2: 3/112: Risk of bias: Low:	

Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 10 years - Actual outcome for Adults with established CVD: All-cause mortality at 2 years; Group 1: 1/111, Group 2: 2/112; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Myocardial infarction at 10 years - Actual outcome for Adults with established CVD: Non-fatal MI at 2 years; Group 1: 1/111, Group 2: 3/112; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospitalisation at 10 years; All-cause mortality at 10 years; CV mortality at 10 years; CV events (MI, Stroke) at 10 years; Stroke/Transient ischaemic attack at 10 years; Sudden cardiac death at 10 years; Sudden cardiac death at 10 years; CV mortality at 10 years; Quality of life at 10 years

Appendix H: Economic evidence tables

H.1 Risk assessment tools

None

H.2 Dietary interventions

Table 67: Dalziel 2006[377]

Dalziel K, Segal L, and de Lorgeril M. A Mediterranean Diet Is Cost-Effective in Patients with Previous Myocardial Infarction. The Journal of Nutrition 136 (7):1879-1885, 2006.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model based on 5 health states and death; transitions to milder states not allowed; 1 year cycles; transition probabilities based on Lyon Diet Heart Study[400-405,1147] and other studies; some probabilities for intervention group applied only for first 4 years (length of Lyon study) **Perspective:** Australia health service [(a)] **Time horizon:** 10 years	**Population:** Patients with an acute myocardial infarction within the previous 6 months. Based on **Cohort settings:** Mean starting age: 54 years Male: 91% **Intervention 1:** Usual dietary advice for cardiac patients **Intervention 2:** Advice from dietitian to adopt a Mediterranean-type diet and supplied with rapeseed margarine (*see clinical evidence*	**Total costs (mean per patient):** Intervention 1: NR [(d)] Intervention 2: NR [(d)] Incremental (2−1): −£135 (CI: NR) **Currency & cost year:** 2003 Australian dollars (presented here as 2003 UK pounds[(e)]) **Cost components incorporated:** Programme costs: consultations with cardiologist and dietitian, written instructions; event costs: costs of hospital treatment for CVD events	**QALYs (mean per patient):** Intervention 1: 6.22 Intervention 2: 6.62 Incremental (2−1): 0.40 (CI: NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates intervention 1 (that is, it is more effective and less costly) **Analysis of uncertainty:** One-way sensitivity analyses were conducted on the base case analysis which used a societal perspective (including food costs), giving results ranging from £198 to £3389 per QALY gained. If similar sensitivity analyses had been conducted on the results from a health service perspective then it would be expected that the intervention would remain dominant under all scenarios except for doubling the number of consultations, which would be

Treatment effect duration[(b)]: 4 years [(c)] **Discounting:** Costs: 5%; Outcomes: 5%	*table above for details*)	(and community treatment for stroke rehabilitation)		expected to produce an ICER of around £228 per QALY gained.
Data sources				
Health outcomes: A review was conducted, which identified 3 studies; the Lyon Diet Heart Study[400-405,1147] (France 1988–1992) was selected as the key source due to its higher quality and particularly longer follow-up. Additional transition probabilities taken from other published studies. **Quality-of-life weights:** Utilities from published literature; tariff unclear, population collected in unclear. **Cost sources:** Resource use based on Lyon Diet Heart Study.[400-405,1147] Australian government unit costs (consultation costs from the Australian Medicare Benefits Schedule, treatment costs from Australian diagnosis-related group costs)				
Comments				
Source of funding: Monash University, Australia and Australian Government Department of Health and Ageing. **Limitations:** Analysis based on a study carried out on patients in France (91% male), and treatment in the Australian health service. Discounting at 5% (3% in a sensitivity analysis). Utility values for quality of life are taken from previous publications. Effectiveness is based on a single RCT (n=605), although this is the only RCT looking at Mediterranean diet in a secondary population included in the clinical review for this question, and so is the best available evidence. Consultation and treatment costs are for the Australian health service in 2003. **Other:** None.				
Overall applicability[(f)]: Partially applicable Overall quality[(g)]: Potentially serious limitations				

Abbreviations: CI: 95% confidence interval; CUA: cost–utility analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years; RCT: randomised controlled trial

(a) The base case analysis of the study takes a societal perspective, including the costs to the participant of buying food. The results presented here relate to sensitivity analysis in which food costs were excluded.

(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long?

(c) For transitions from the initial health state ('alive free of further events') to other states, different transition probabilities were applied to the control (intervention 1) and diet (intervention 2) groups for the first 4 years, in line with the length of the Lyon Diet Heart Study. After 4 years the transition probabilities for the diet group reverted to the same values as for the control group. For transitions between other states the same transition probabilities were used for both groups throughout the course of the model.

(d) The total costs of each strategy are not explicitly stated in the paper for the sensitivity analysis excluding food costs. However, assuming that these would be the same as the totals including food costs, minus the food costs (both given in Table 4 of the paper) gives £1210 for intervention 1 and £1078 for intervention 2. This implies an incremental cost of –£132, which is close to, but not quite equal to the –£135 incremental cost stated.

(e) Converted using 2003 purchasing power parities[1056]

(f) Directly applicable / Partially applicable / Not applicable

(g) Minor limitations / Potentially serious limitations / Very serious limitations

H.3 Foods enriched with phytosterols (plant stanols and sterols)

None

H.4 Efficacy of statin therapy

Table 68: Ara 2009[100,101]

Ara R, Pandor A, Stevens J, Rees A, and Rafia R. Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation. Health Technology Assessment 13(34):1-118, 2009. **Also summarised in: Ara R, Pandor A, Stevens J, Rafia R, Ward S E, Rees A et al. Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: Is this a cost-effective strategy? European Journal of Preventive Cardiology 19(3):474-483, 2012.**				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model of CVD states with 1-year cycles (adaptation of model in Ward 2005) **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration**[(a)]**:** lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** UK patients with existing ACS (angina, MI, revascularisation) **Cohort settings:** Start age: 60 Male: NR **Intervention 1:** Medium intensity statin: simvastatin 40 mg daily **Intervention 2:** High intensity statins **Intervention 2a:** Simvastatin 80 mg daily **Intervention 2b:** Atorvastatin 80 mg daily **Intervention 2c:** Rosuvastatin 40 mg daily	**Total costs (mean per patient):** Intervention 1: £14,522 Intervention 2a: £15,110 Intervention 2b: NR [(b)] Intervention 2c: £18,464 Incremental (2a−1): £588 Incremental (2b−1): NR[(b)] Incremental (2c−1): £3941 (95% CI: NR; p=NR in all cases) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Statins. Consultations and monitoring tests. CV event health states for Markov model (first and subsequent years):	**QALYs (mean per patient):** Intervention 1: 7.546 Intervention 2a: 7.657 Intervention 2b: NR [(b)] Intervention 2c: 7.862 Incremental (2a−1): 0.111 Incremental (2b−1): NR[(b)] Incremental (2c−1): 0.316 (95% CI: NR; p=NR in all cases)	**ICERs** **Intervention 2a versus Intervention 1:** £5319 per QALY gained (pa) (95% CI: £5229 to £5408) **Intervention 2b versus Intervention 1:** £3172 per QALY gained (pa/da – unclear) (95% CI: NR) **Intervention 2c versus Intervention 1:** £12,484 per QALY gained (pa) (95% CI: £12,372 to £12,595) **Intervention 2b versus Intervention 2a:** Atorvastatin 80 mg dominates simvastatin 80 mg **Intervention 2c versus Intervention 2b:** ICER cannot be calculated using data reported,[(b)] but it is stated that atorvastatin 80 mg is the preferred, cost effective treatment where the cost-effectiveness threshold is between £5000 and £30,000 per QALY gained.

		unstable angina, MI, revascularisation, stroke.		**Analysis of uncertainty:** The base case scenario, with a high cost of atorvastatin (in which it was found that all 3 high intensity statins were cost effective compared to simvastatin 40 mg, with rosuvastatin 40 mg dominating atorvastatin 80 mg and cost effective compared to simvastatin 80 mg), was subject to one-way sensitivity analyses with regard to discounting (0%), starting age (50, 70), health state costs (±50%) and utility values (±20%) and was robust to all these – the ICER for rosuvastatin (£12,484 in the base case) remained below £20,000 in each case. High-intensity statins were however dominated by medium-intensity statins when the relative clinical effectiveness of medium- and high-intensity statins was varied substantially. These sensitivity analyses were not applied when the cost of atorvastatin was reduced (as that was itself a sensitivity analysis), though it could be predicted that the results would similarly be relatively robust to varying most parameters apart from clinical effectiveness. Different patterns of adherence to statins were also studied, but these also had only moderate effect on cost effectiveness, both in the base case and for reduced cost (£92) atorvastatin – with the ICER varying between £3155 and £7331 with different assumptions regarding adherence to statins. The analysis was also repeated with a third, lower possible atorvastatin cost of £20.78 per year. The ICER was not stated, but at this cost atorvastatin was the preferred, cost-effective intervention at all cost-effectiveness thresholds.
Data sources				

Health outcomes: Baseline event rates taken from large UK registry studies (NHAR, RITA-2, SLSR), similar to Ward 2005. Effectiveness from meta-analysis and network meta-analysis of 28 phase III trials measuring effect of statins on LDL cholesterol. Cholesterol reduction converted into CV events using CTT 2005.[131] **Quality-of-life weights:** Various published sources using EQ-5D in UK. **Cost sources:** Health state costs from Ward 2005 or calculated from BNF prices using new assumptions on resource use. Simvastatin and rosuvastatin costs from BNF (2008). Atorvastatin cost estimated future cost for generic drug.
Comments
Source of funding: UK National Coordinating Centre for Health Technology Assessment. **Limitations:** Based on UK ACS population, following NICE reference case. Model does not account for adverse events. Effectiveness of statins in reducing CV events is based on a meta-analysis of effectiveness in reducing LDL cholesterol, linked to relationship between cholesterol reduction and CV event reduction - necessary at the time due to lack of direct evidence for rosuvastatin, but not as good as direct evidence. Cost of atorvastatin 80 mg assumed to fall to £92 or £20.78 annually once off patent; actual current cost is £32.35. **Other:** None
Overall applicability[(c)]**:** Directly applicable **Overall quality**[(d)]**:** Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; ACS: acute coronary syndrome; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Costs and outcomes were given for the intervention (£18,572, 7.778 QALYs) and incrementally (£4,050, 0.232 QALYs – ICER £17,469) for the base case used in the paper (atorvastatin 80 mg at full price: £367.76 per year), but not for the sensitivity analysis for atorvastatin 80 mg at £92 per year (or the additional analysis using £20.78 per year), which are the analyses of primary interest to this review.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Table 69: Choudhry 2011[314]

Choudhry N K, Patrick A R, Glynn R J, and Avorn J. The cost-effectiveness of C-reactive protein testing and rosuvastatin treatment for patients with normal cholesterol levels. Journal of the American College of Cardiology 57(7):784-791, 2011.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:**	**Population:** Men ≥50 years old and woman ≥60 years old with LDL cholesterol levels of <130 mg/dl (3.36 mmol/litre) and no known cardiovascular disease.	**Total costs (mean per patient):** Intervention 1: £12,884 Intervention 2: £18,045 Incremental (2−1): £5161 (95% CI NR; p=NR) **Currency & cost year:**	**QALYs (mean per patient):** Intervention 1: 10.29 Intervention 2: 10.61 Incremental (2−1): 0.31 (95% CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £16,465 per QALY gained (da) £18,018 per QALY gained (95% CI: £6796 to £41,024) (pa) Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:**

Decision tree to decide who was treated followed by a Markov model comprising of 33 health states. Relative treatment effect applies to the probability of moving between states with a 1 year cycle length. **Perspective:** US health and social care **Time horizon:** Lifetime **Treatment effect duration**[(a)]**:** Lifetime **Discounting:** Costs: 3%; Outcomes: 3%	**Cohort settings:** Start age: same as JUIPTER trial participants Male: same as JUIPTER trial participants **Intervention 1:** usual care (no statins) **Intervention 2:** Testing hs-CRP levels followed by rosuvastatin 20 mg for patients with hs-CRP levels ≥2.0 mg/litre	2009 US dollars (presented here as 2009 UK pounds[(b)]) **Cost components incorporated:** Costs associated with treatment and monitoring: hs-CRP test, liver function test, rosuvastatin. Costs associated with events: MI, unstable angina, revascularisation, stroke, pulmonary embolism, deep vein thrombosis, myopathy, elevated liver enzymes, diabetes.		The study conducted a series of one-way and two-way sensitivity analyses. In the one-way sensitivity analyses the ICER increased above the £20,000 threshold in the following scenarios: statins have a lower effect on vascular diseases (lower bound of 95% CI reported in JUPITER trial); statins have a higher effect on adverse events (upper bound of 95% CI reported in JUPITER trial); duration of treatment effect falls to 15 years; assuming the patent never expires; adding a disutility of 0.02 associated with daily statin use. In the two-way sensitivity analyses the ICER increased above the £20,000 threshold in the following scenarios: statin efficacy falls below approximately 63% of efficacy in JUPITER and daily rosuvastatin price is higher than £1.63 (£597/year); daily rosuvastatin price is above £0.98 (£358/year) and patients have a Framingham risk score of <10%.
Data sources				
Health outcomes: Baseline and effectiveness data from the JUPITER trial.[1153] **Quality-of-life weights:** Taken from various published sources. **Cost sources:** Treatment costs from Medicare and other US hospital costs. Rosuvastatin based on branded US cost for first 7 years (£866/year) but assumed to decrease to £239/year after 8 years when rosuvastatin is due to come off patent, compared to current UK cost of £339/year.				
Comments				
Source of funding: One author received a research grant from AstraZeneca (manufacturer of rosuvastatin) for working on the JUPITER trial. The authors' hospital holds patents relating to using hs-CRP testing in evaluating patients' CV risk. **Limitations:** Based on a population with low CV risk but high levels of high-sensitivity C-reactive protein. The treatment decision in this model is based on hs-CRP level. It is unclear how this relates to a general UK primary prevention population at specified CV risk levels. Based on the US healthcare system. Baseline event rate based on JUPITER study not UK primary population. Effectiveness of rosuvastatin based on JUPITER study not a meta-analysis of multiple studies. Resource use and costs of based on the US healthcare system. Initial cost of rosuvastatin 20 mg based on US costs (higher than current UK cost), but assumed to fall below current UK costs once rosuvastatin comes off patent. **Other:** None				

Overall applicability[(c)]**:** Partially applicable	**Overall quality**[(d)]**:** Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; CV: cardiovascular; ICER: incremental cost-effectiveness ratio; hs-CRP: high-sensitivity C-reactive protein; MI: myocardial infarction; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2009 purchasing power parities[1056]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Table 70: Erickson 2013[469]

Erickson K F, Japa S, Owens D K, Chertow G M, Garber A M, and Goldhaber-Fiebert J D. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. J Am Coll Cardiol 61(12):1250-1258, 2013.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model with 3-month cycles including progression through both CVD and CKD states. **Perspective:** US healthcare **Time horizon:** Lifetime **Treatment effect**	**Population:** People with mild-to-moderate CKD and moderate hypertension (base case). **Cohort settings:** Start age: 65 (base case) Sex: separate male and female cohorts **Intervention 1:** No treatment **Intervention 2:** Statins as a single class	**Total costs (mean per patient):** Intervention 1: £0 Intervention 2: £1244 Incremental (2−1): £1244 (95% CI: NR; p=NR) **Currency & cost year:** 2010 US dollars (presented here as 2010 UK pounds[(b)]) **Cost components incorporated:** Statins: used an annual cost for generic pravastatin 40 mg (£33), similar to current UK statin costs (£10–£32) Healthcare: costs of treating MI, stroke, rhabdomyolysis;	**QALYs (mean per patient):** Intervention 1: 0 QALYs Intervention 2: 0.10 QALYs Incremental (2−1): 0.10 QALYs (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £12,440 per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£34,556 threshold): 99% **Analysis of uncertainty:** Base case related to 65 year old men. For 65 year old women ICER=£23,084 Treatment is cost effective at a threshold of £34,556 in 99% of probabilistic simulations for 65 year old or 50 year old men and 94% for 65 year old women, but 38% for 50 year old women. Treatment is less cost effective for those with more advanced CKD, those with lower baseline CV risk, and younger patients. Results were very sensitive to the risk of rhabdomyolysis which may be higher in those with CKD. If statins slow CKD progression as well as CVD

duration[(a)]**:** Lifetime **Discounting:** Costs: 3%; Outcomes: 3%		CKD (by stage)		progression then they would be cost saving.
Data sources				
Health outcomes: Baseline CKD progression data from large cohorts; baseline probabilities of MI and stroke calculated from Framingham risk scores and multiplied by hazard ratios relating to CKD stage. Effectiveness of statin treatment taken from Cochrane meta-analysis of statin trials in people with CKD,[1011] with reduced effectiveness in CKD stage 4 in line with SHARP trial, and no effectiveness in CKD stage 5. **Quality-of-life weights:** Taken from published literature (CKD weights from Gorodetskaya 2005, CVD from Tengs 2000). **Cost sources:** Statin costs from generic pravastatin 40 mg available from US discount retailers. Treatment costs from published sources based on US managed care and Medicare reimbursements.				
Comments				
Source of funding: US government (AHRQ, Department of Veterans Affairs). **Limitations:** Assesses all statins in a single class, so no judgement can be made on the relative cost effectiveness of different intensity statins. Model relates largely to the US healthcare system. Model uses a somewhat simplified model of CVD, though this does allow CKD stages to be included at the same time. A variety of sources of US costs are used, which may not be entirely consistent and would not be relevant for a UK NHS context. **Other:** None.				
Overall applicability[(c)]**:** Partially applicable **Overall quality**[(d)]**:** Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2010 purchasing power parities[1056]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Table 71: McConnachie 2014[940]

McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard C J et al. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. European Heart Journal. 35(5):290-298, 2014.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** within-trial	**Population:** Men in West Scotland with raised cholesterol but no previous MI (primary prevention)	**Total costs (mean per patient):** Intervention 1: £3550 Intervention 2: £2840	**QALYs (mean per patient):** Intervention 1: 11.057 Intervention 2: 11.193 Incremental (2−1): 0.136	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates Intervention 1 (is cheaper and more effective) – cost saving of £710 per person over 15 years.

analysis **Approach to analysis:** 10-year follow up of participants in 5-year WOSCOPS[1249] trial, looking at healthcare usage **Perspective:** UK NHS **Follow-up:** 15 years **Treatment effect duration**[(a)]**:** 5 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Start age: 45–64 Male: 100% **Intervention 1:** No statins during trial (4.9 years); after 5 years additional follow up 35.2% taking LLT **Intervention 2:** Pravastatin 40 mg daily during trial (4.9 years); after 5 years additional follow up 38.7% taking LLT	Incremental (2−1): −£710 (95% CI: −£1090 to −£320; p<0.001) **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** Statins (pravastatin 40 mg). Consultations and monitoring tests. Healthcare: costs of hospital admissions for any CV or diabetes-related cause; costs of continuing treatment for people with CV conditions	(95% CI: 0.025 to 0.247; p=0.017)	Probability Intervention 2 cost-effective (£20K/30K threshold): N/A **Analysis of uncertainty:** One-way sensitivity analyses showed that the intervention was still cost saving if hospital costs or ongoing costs of CV events were varied by ±25%. If statin and monitoring costs were increased by 400% then it was no longer cost saving but still highly cost effective.
Data sources				
Health outcomes: CV events and hospital admissions based on linked healthcare records for WOSCOPS participants for control and intervention groups. **Quality-of-life weights:** Uses disutilities of CV conditions from Ward 2005 – various sources. **Cost sources:** Used 2012 UK annual cost of generic pravastatin 40 mg (£36), similar to current UK cost (£23). Hospital costs based on NHS Scotland Tariff costs for HRGs. Continuing costs of CV conditions based on Ward 2005.				
Comments				
Source of funding: Original WOSCOPS trial and first 5 years follow up funded by Bristol-Myers Squibb (manufacturer of pravastatin). This further follow-up study was not funded by manufacturer (Wellcome Trust, Celera Diagnostics). **Limitations:** Looks at Scottish men aged 45–54 at start. Follows NICE reference case where possible. Utility values taken from Ward. Baseline event rate based on the WOSCOPS study not a meta-analysis or whole UK epidemiology – reflects men aged 45–54 in West Scotland, but likely to be relatively similar to men throughout UK. Effectiveness of pravastatin based on WOSCOPS not meta-analysis of multiple trials, but WOSCOPS was carried out in UK and so is highly relevant. Uses real-life NHS resource use over 15 year follow up, applying current NHS HRG costs and recent cost of pravastatin. **Other:** None				
Overall applicability[(b)]**:** Directly applicable **Overall quality**[(c)]**:** Minor limitations				

Abbreviations: CUA: cost–utility analysis; CV: cardiovascular; da: deterministic analysis; HRG: healthcare resource group; ICER: incremental cost-effectiveness ratio; LLT: lipid-lowering therapy; N/A: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 72: NCCPC 2008[1003]

National Collaborating Centre for Primary Care. A model to estimate the cost-effectiveness of higher versus lower intensity statins in the treatment of coronary heart disease. In: Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease, NICE Clinical Guideline 67. National Institute for Health and Clinical Excellence, 2008, Appendix C, pp47-69.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model of CVD states with 6-month cycles (adaptation of model in Ward 2005) **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration**[(a)]**:** lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** UK secondary prevention. Separate analyses for: A: ACS (high risk) B: CHD (lower risk) **Cohort settings:** Start age: 65 Male: NR **Intervention 1:** Lower-intensity statins (effectiveness data from atorvastatin 10 mg, simvastatin 20 mg (both medium intensity) and pravastatin 40 mg (low intensity)) **Intervention 2:** High-intensity statins:	**Total costs (mean per patient):** A: ACS Intervention 1: £10,165 Intervention 2: £11,583 Incremental (2−1): £1418 (95% CI: NR; p=NR) B: CHD Intervention 1: £7692 Intervention 2: £10,081 Incremental (2−1): £2389 (95% CI: NR; p=NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Statins. Consultations and	**QALYs (mean per patient):** A: ACS Intervention 1: 5.52 Intervention 2: 5.84 Incremental (2−1): 0.32 (95% CI: NR; p=NR) B: CHD Intervention 1: 5.61 Intervention 2: 5.70 Incremental (2−1): 0.08 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** A: ACS £4397 per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): 94%/NR B: CHD £28,361 per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): 42%/NR **Analysis of uncertainty:** Both conclusions (high-intensity statins are cost effective at a threshold of £20,000 per QALY for ACS but not for CHD) were robust to one-way sensitivity analyses varying effectiveness of treatment (varying one outcome at a

	atorvastatin 80 mg (or simvastatin 80 mg)	monitoring tests. CV event health states for Markov model (first and subsequent years): unstable angina, MI, TIA, stroke, PAD, HF, revascularisation.		time) apart from CV death, age, cost of CV event states, utilities, and number of consultations. The results were sensitive to the cost of statins, with high-intensity treatment dominating lower-intensity statins for CHD patients when the cost of simvastatin 80 mg is used instead of atorvastatin 80 mg, assuming equal effectiveness.
Data sources				
Health outcomes: Baseline data from combination of UK epidemiology, UK cohort studies (including NHAR, SLSR) and international trials. Generally best available sources, though may now be partially out of date due to developments in standard treatment for CV events. Effectiveness based on meta-analysis of the available head-to-head trials (PROVE IT and A to Z for ACS; IDEAL and TNT for CHD). **Quality-of-life weights:** Various published sources, mainly patient-reported using EQ-5D in UK, identified in a systematic review (by Ward 2005). **Cost sources:** Statins UK 2008 costs. Health states based on Ward 2005, other NICE guidelines and NHS reference costs.				
Comments				
Source of funding: NICE. **Limitations:** Designed in accordance with NICE reference case. The costs used, especially for statins, are now out of date, making the results unreliable. This is unlikely to affect the conclusion favouring high-intensity statins for higher risk (ACS) secondary prevention patients, but is likely to change the conclusion favouring lower-intensity statins for lower risk (CHD) secondary prevention patients. **Other:** None				
Overall applicability[(b)]**:** Directly applicable **Overall quality**[(c)]**:** Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; ACS: acute coronary syndrome; CHD: coronary heart disease; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HF: heart failure; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; PAD: peripheral artery disease; QALYs: quality-adjusted life years; TIA: transient ischaemic attack

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 73: Ward 2005[1405,1408]

Ward S, Lloyd Jones M, Pandor A, Holt J M, Ara R, Ryan A et al. Statins for the Prevention of Coronary Events: Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. National Institute for Health and Clinical Excellence. 2005.
Also published as: Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A et al. A systematic review and economic evaluation of statins for the prevention of

coronary events. Health Technology Assessment 11(14):1-322, 2007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model of CVD states with 1-year cycles. Run separately for primary and secondary prevention. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration**[a]**:** lifetime **Discounting:** Costs: 6.0%; Outcomes: 1.5%	**Population:** A: UK secondary population (all risk levels combined) B: UK primary population, grouped by annual CHD risk **Cohort settings:** Start age: presented for 45, 55, 65, 75, 85 with no single base case. Results for 65 are presented here Male: 100% [0%] **Intervention 1:** No treatment **Intervention 2:** Statin treatment (all statins as a single class)	**Total costs (mean per patient)**[b]**:** A: Secondary, male [female] Intervention 1: NR Intervention 2: NR Incremental (2−1): £3218 [£3562] (95% CI: NR; p=NR) B: Primary, 1.5% annual CHD risk, male [female] Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR) **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** Statins. Consultations and monitoring tests. CV event health states for Markov model (first and subsequent years): stable angina, unstable angina, MI, TIA, stroke.	**QALYs (mean per patient)**[b]**:** A: Secondary, male [female] Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.314 [0.387] (95% CI: NR; p=NR) B: Primary, 1.5% annual CHD risk, male [female] Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1)**[b]**:** A: Secondary, male [female] £9100 [£8,400] per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): NR/NR B: Primary, 1.5% annual CHD risk, male [female] £11,200 [£9,600] per QALY gained (da) (95% CI: NR) Probability Intervention 2 cost-effective (£20K/30K threshold): NR/NR **Analysis of uncertainty:** Probabilistic results are very similar to deterministic results. ICERs for secondary prevention are below £14,000 for all age and sex subgroups. ICERs for primary prevention increase with age – statins are not cost effective at age 85 at 1.5% CHD risk (or 2.0% risk in men). Additional sensitivity analyses conducted on the base case analysis looking at only CHD events (rather than the CVD results presented here) showed that primary and secondary results were sensitive to the use of 3.5% discount rates, low compliance and shortened (10 year)

				effectiveness.
Data sources				
Health outcomes: Baseline data from combination of UK epidemiology, UK cohort studies (including NHAR, SLSR) and international trials. Generally best available sources, though may now be partially out of date due to developments in standard treatment for CV events. Effectiveness based on a meta-analysis of 48 statin versus placebo trials. **Quality-of-life weights:** Various published sources, mainly patient-reported using EQ-5D in UK, identified by a systematic review. **Cost sources:** Statins UK 2004 costs, weighted by frequency of use in the trials. Health state costs based on previous studies[321,1066,1470] or calculated using NHS medication and reference costs based on expert assumptions of resource use.				
Comments				
Source of funding: NICE. **Limitations:** Designed in accordance with the then-current NICE reference case. However, that specified discount rates of 6% for costs and 1.5% for benefits, which differ from the current preferred discount rates of 3.5% for both costs and benefits. The study carried out some sensitivity analyses using 3.5% discount rates; had these been the base case analyses, some of the conclusions of the study would have been different. The costs used, especially for statins, are now out of date, making the results unreliable. This is unlikely to affect the conclusions that statins are cost effective for secondary prevention or for primary prevention in at least some cases, but would be expected to change the conclusion regarding where the risk threshold for treatment for primary prevention should be. **Other:** None				
Overall applicability[(c)]**:** Partially applicable **Overall quality**[(d)]**:** Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; ACS: acute coronary syndrome; CHD: coronary heart disease; CUA: cost–utility analysis; CVD: cardiovascular disease; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HF: heart failure; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; pa: probabilistic analysis; PAD: peripheral artery disease; QALYs: quality-adjusted life years; TIA: transient ischaemic attack

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) This study includes a base case looking only at the effects of statins in reducing CHD events, and additional scenarios which look at reducing CVD events, adding in some or all effects of reducing stroke and TIA as well. The results presented here are for the scenario including all CVD events.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

H.5 Adherence to statin therapy

None

H.6 Statins: predictors of adverse events

None

H.7 Fibrates for prevention of CVD

Table 74: Nyman 2002[1035]

Nyman JA, Martinson MS, Nelson D et al. Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol. Archives of Internal Medicine. 2002; 162:177-182				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model using risks of experiencing, dying from and recovering from major CV events (MI, stroke), and risk of death. Hazard functions calculated for transition rates. The only rate altered by treatment was annual risk of experiencing an event. Annual cycles. **Perspective:** USA Veterans Affairs healthcare system **Time horizon:** Lifetime **Treatment effect duration[(a)]:** 5 years **Discounting:** Costs: 3%; Outcomes: 3% (sensitivity analysis)	**Population:** Cohort based on VA-HIT patients:[1172-1174] men <74 years, history of CHD, HDL-C level ≤1.03mmol/l, LDL-C level ≤3.6mmol/l), no severe comorbidity (patients with diabetes and hypertension included) **Cohort settings:** Start age: calculated for 55 years, 65 years, 75 years Male: 100% **Intervention 1:** Placebo, 5 years **Intervention 2:** Gemfibrozil 1.2g/day, 5 years	**Total costs (mean per patient):** Intvn 1: £4778 Intvn 2: £7157 Incremental (2-1): £2379 (CI NR; p=NR) **Currency & cost year:** 1998 US dollars (presented here as 1998 UK pounds[(b)]) **Cost components incorporated:** Drugs, annual lipid monitoring test, hospital costs of treatment of cardiovascular events	**QALYs (mean per patient):** Intervention 1: 11.17 QALYs (12.69 life years) Intervention 2: 11.51 QALYs (13.07 life years) Incremental (2-1): 0.34 QALYs (0.38 life years) (CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £6998 per QALY gained (£6261 per life year gained) (da) (CI NR) **Analysis of uncertainty:** Hazard functions used for transition rates. Deterministic costs and utility used. Cost effectiveness was calculated for patients starting the model at 55 years, 65 years, 75 years. Sensitivity analyses were carried out for discount rates of 0%, 3%, 5%; drugs at reduced price (£30/year) or wholesale price (£617/year); and a utility for people with CHD of 0.88 or 1.00. The results detailed above are for the case of 65 years, 3% discounting, wholesale price, utility of 0.88 (life years represents utility of 1.00). For drugs at reduced price the intervention was cost saving in all scenarios. For drugs at wholesale prices the intervention gave ICERs of £6325 (75 years) to £8254 (55 years) per QALY gained with 3% discounting and utility of 0.88. Sensitivity analyses were also carried out using log normal or Weibull functions for the hazard functions. The full results of these were not published, but they led to a wider range of values.

Data sources
Health outcomes: Within-trial analysis (VA-HIT). Baseline risk from placebo arm; relative treatment effect from intervention arm. **Quality-of-life weights:** Alternative utility value of 0.88 taken from 1 previous study,[1354] which derived it using self-reported time trade-off with 67 post-MI patients. This study applied that to all patients, before and after any CV events. **Cost sources:** Drug cost from trial and US wholesale price. Resource use from within-trial patient-level analysis. Unit costs from US DRG costs.
Comments
Source of funding: Veterans Affairs, with supplementary grant from Parke-Davis which manufactured branded gemfibrozil. **Limitations:** Significant uncertainty about the applicability of US resource use and costs from 1998. Changes in cardiac treatments since this study further reduce the applicability of the treatment costs. Current UK drug costs (£453/year) are between the 2 prices used in the study and so would tend to reduce the ICERs quoted for full cost drugs. Different treatment costs in a current UK situation would also alter the cost effectiveness, with an increase in those costs also making these results conservative, but a decrease in treatment costs making these results underestimates. Uniform utility values are used for all patients, which is unrealistic, but the results are not greatly affected by changes to the utility values. These results are applicable to the specific subpopulation studied, but are not applicable to secondary prevention populations in general. The model does not consider the effects on cost or HRQoL of adverse events. The results are robust to the sensitivity analyses performed, but sensitivity analysis was not performed on treatment costs. Some funding was from the manufacturer of branded gemfibrozil. **Other:** None.
Overall applicability[(c)]: Partially applicable **Overall quality[(d)]:** Potentially serious limitations

Abbreviations: CI: 95% confidence interval; CUA: cost–utility analysis; CV: cardiovascular; da: deterministic analysis; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; NR: not reported; QALYs: quality-adjusted life years; SD: standard deviation

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 1998 purchasing power parities[1056]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations /Potentially serious limitations / Very serious limitations

H.8 Nicotinic acid for the prevention of CVD

None

H.9 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

None

H.10 Omega-3 fatty acid compounds for the prevention of CVD

None

Appendix I: Forest plots

I.1 Risk assessment tools

I.1.1 AUC for non-diabetic population

Figure 11: Head-to-head comparison of QRISK2 versus NICE-Framingham in the QRESEARCH cohort

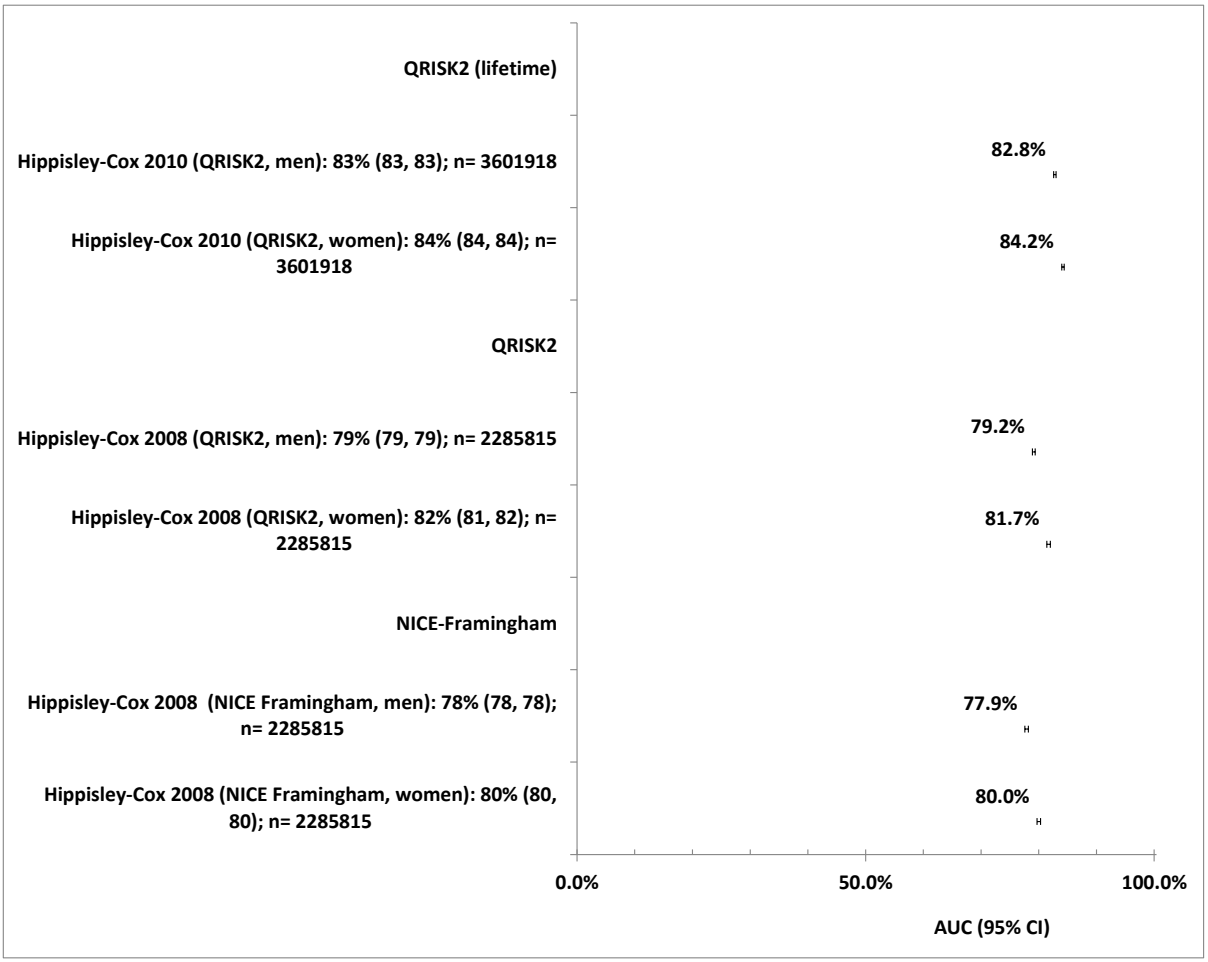


Figure 12: Head-to-head comparison of QRISK2 versus NICE-Framingham in the THIN cohort

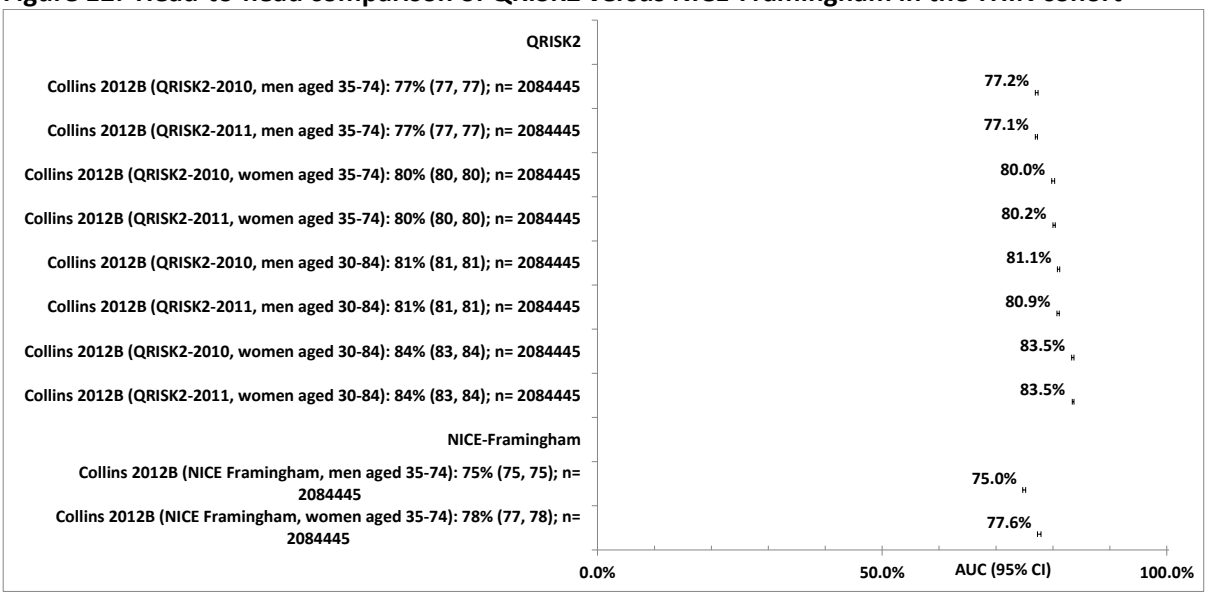
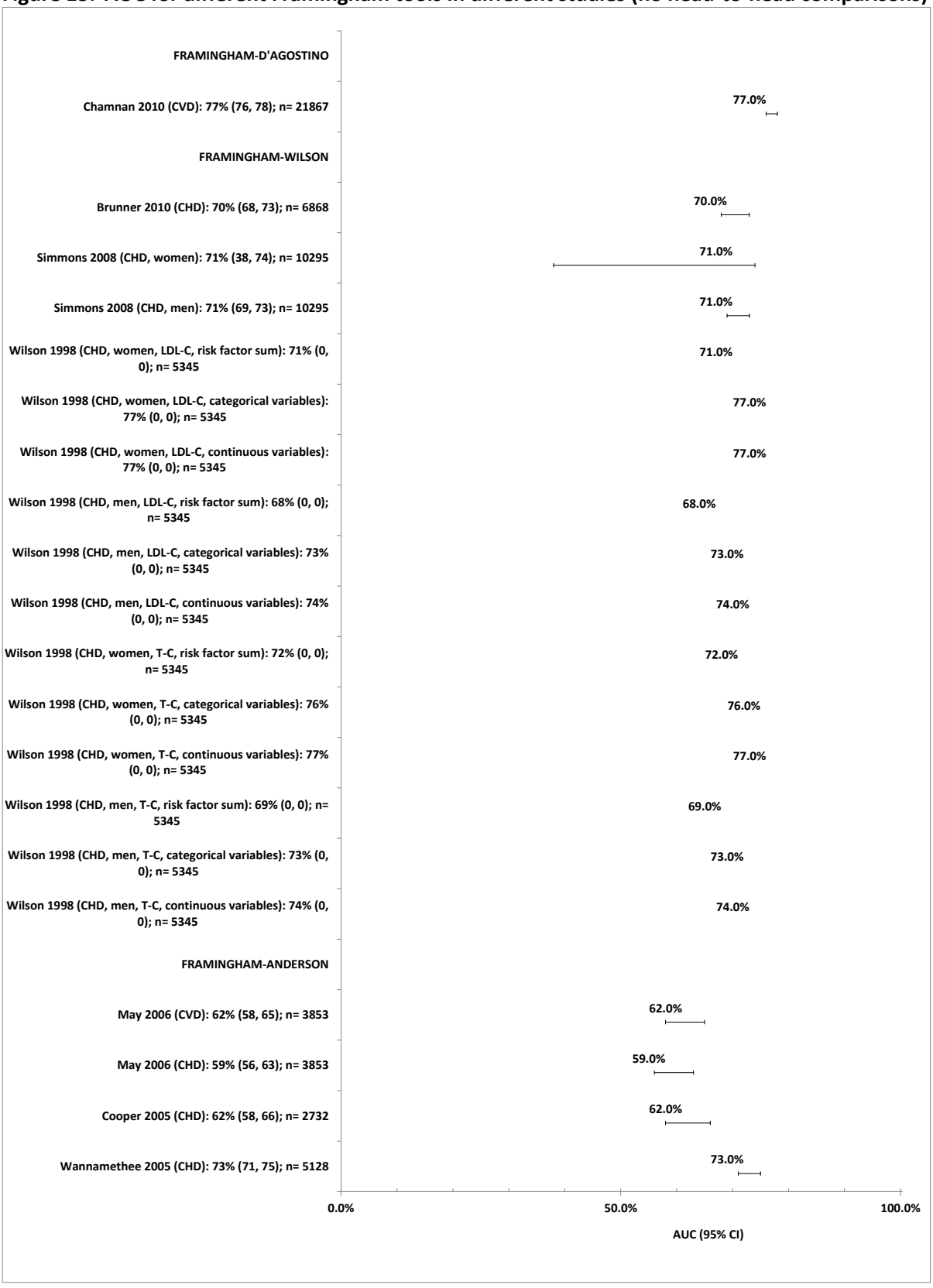
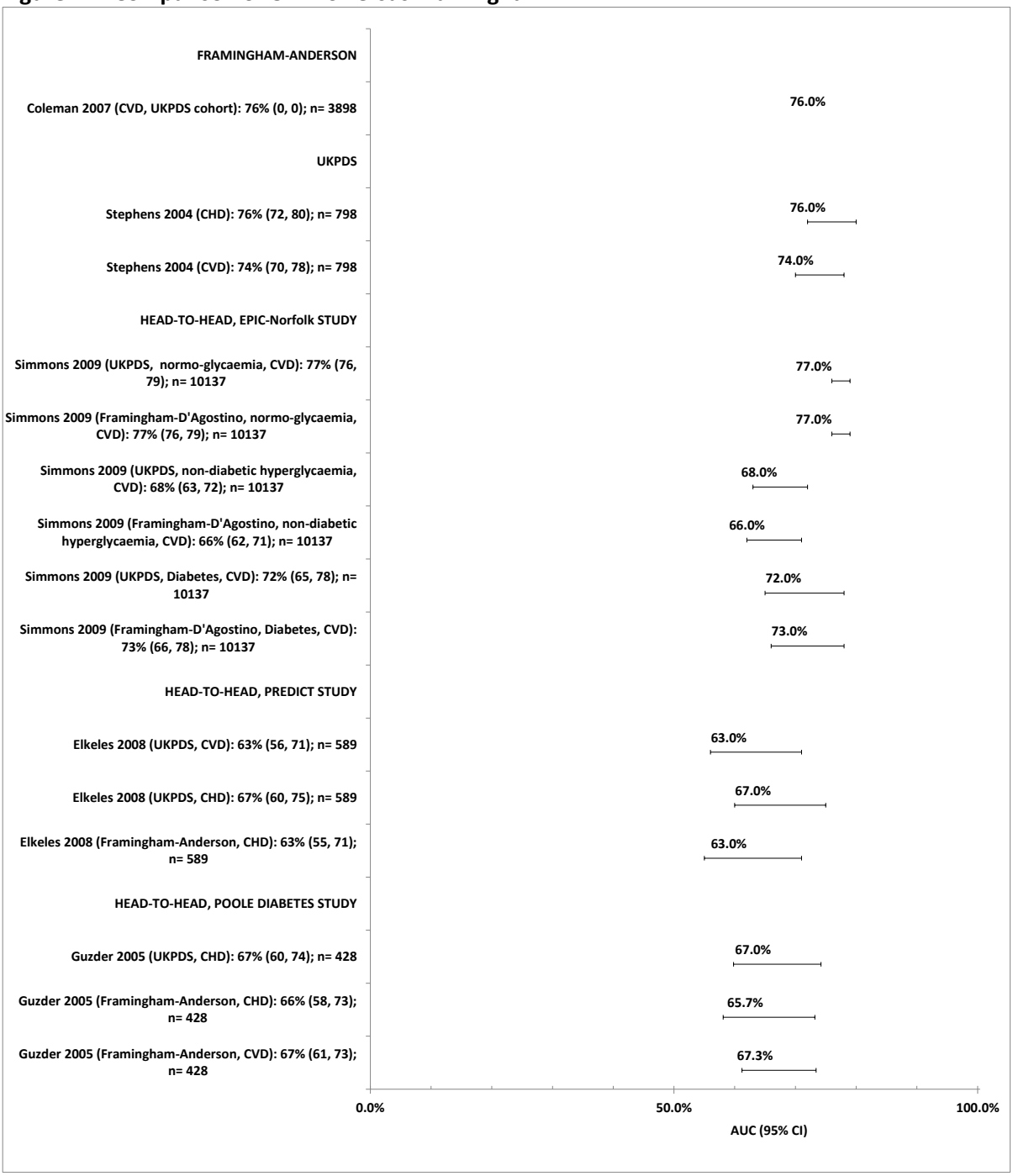


Figure 13: AUC for different Framingham tools in different studies (no head-to-head comparisons)



I.1.2 AUC in diabetic population

Figure 14: Comparison of UKPDS versus Framingham



I.1.3 Sensitivity and specificity in non-diabetic population

Figure 15: Sensitivity and specificity for Framingham, QRISK2 and age alone, at specified thresholds

Framingham (30%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Brindle 2003	106	338	571	4152	0.16 [0.13, 0.19]	0.92 [0.92, 0.93]
Chamnan 2010	916	2398	1297	17256	0.41 [0.39, 0.43]	0.88 [0.87, 0.88]
Jones 2001	67	14	33	577	0.67 [0.57, 0.76]	0.98 [0.96, 0.99]
May 2006 (CHD)	20	169	178	3215	0.10 [0.06, 0.15]	0.95 [0.94, 0.96]
May 2006 (CVD)	91	702	149	2640	0.38 [0.32, 0.44]	0.79 [0.78, 0.80]

Framingham (20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chamnan 2010	1494	5189	719	14465	0.68 [0.66, 0.69]	0.74 [0.73, 0.74]
Ramsay 2011 (Manual)	219	907	202	2454	0.52 [0.47, 0.57]	0.73 [0.71, 0.75]
Ramsay 2011 (Non-manual)	123	518	97	1947	0.56 [0.49, 0.63]	0.79 [0.77, 0.81]
Wald 2011	307	858	158	8677	0.66 [0.62, 0.70]	0.91 [0.90, 0.92]

Framingham (15%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Brindle 2003	508	2020	169	2470	0.75 [0.72, 0.78]	0.55 [0.54, 0.56]
Chamnan 2010	1755	7626	458	12028	0.79 [0.78, 0.81]	0.61 [0.61, 0.62]
Jones 2001	244	24	52	371	0.82 [0.78, 0.87]	0.94 [0.91, 0.96]
Simmonds 2012	367	1907	98	7628	0.79 [0.75, 0.83]	0.80 [0.79, 0.81]

Age alone (66 yrs cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wald 2011	307	1144	158	8391	0.66 [0.62, 0.70]	0.88 [0.87, 0.89]

Framingham (8%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wald 2011	400	2002	65	7533	0.86 [0.83, 0.89]	0.79 [0.78, 0.80]

Age alone (55 yrs cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wald 2011	400	2288	65	7247	0.86 [0.83, 0.89]	0.76 [0.75, 0.77]

Framingham (5%)

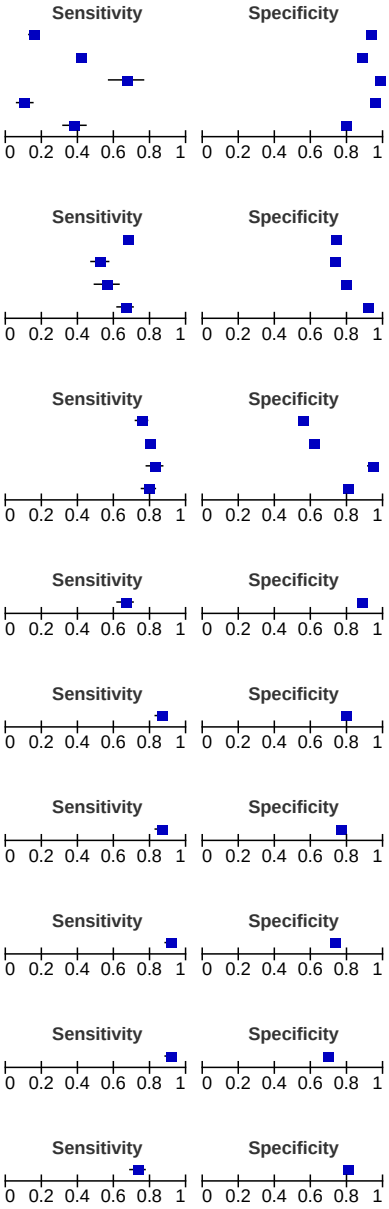
Study	TP	FP	FN	TN	Sensitivity	Specificity
Wald 2011	423	2574	42	6961	0.91 [0.88, 0.93]	0.73 [0.72, 0.74]

Age alone (50 yrs cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Wald 2011	423	2956	42	6579	0.91 [0.88, 0.93]	0.69 [0.68, 0.70]

QRISK2

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmonds 2012	339	1907	126	7628	0.73 [0.69, 0.77]	0.80 [0.79, 0.81]



I.1.4 Sensitivity and specificity in diabetic population (type 2 diabetes)

Figure 16: Sensitivity and specificity for Framingham and UKPDS, at specified thresholds

Framingham (diabetes, 30%, T-C>5mmol/l)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	29	38	69	292	0.30 [0.21, 0.40]	0.88 [0.85, 0.92]

UKPDS (diabetes, 30%, T-C>5mmol/l)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	49	102	49	228	0.50 [0.40, 0.60]	0.69 [0.64, 0.74]

Framingham (diabetes, 15%, T-C>5mmol/l)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	71	181	27	149	0.72 [0.63, 0.81]	0.45 [0.40, 0.51]

UKPDS (diabetes, 15%, T-C>5mmol/l)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	75	177	23	153	0.77 [0.67, 0.85]	0.46 [0.41, 0.52]

Framingham (diabetes, 15%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	84	221	14	109	0.86 [0.77, 0.92]	0.33 [0.28, 0.38]

UKPDS (diabetes, 15%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Guzder 2005	87	230	11	100	0.89 [0.81, 0.94]	0.30 [0.25, 0.36]

Framingham (diabetes, 20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	59	142	10	61	0.86 [0.75, 0.93]	0.30 [0.24, 0.37]

UKPDS (diabetes, 20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	65	140	4	63	0.94 [0.86, 0.98]	0.31 [0.25, 0.38]

Framingham (non-diabetes hyperglycaemia, 20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	144	552	16	194	0.90 [0.84, 0.94]	0.26 [0.23, 0.29]

UKPDS (non-diabetes hyperglycaemia, 20%)

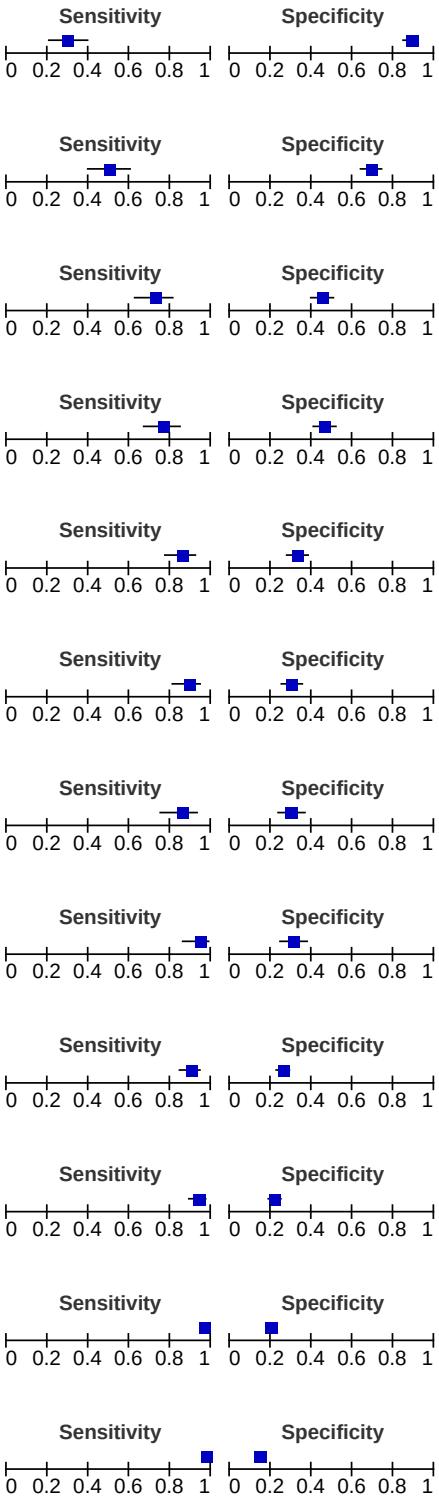
Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	150	582	10	164	0.94 [0.89, 0.97]	0.22 [0.19, 0.25]

Framingham (normo-glycaemic, 20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	870	6442	36	1611	0.96 [0.95, 0.97]	0.20 [0.19, 0.21]

UKPDS (normo-glycaemic, 20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Simmons 2009	879	6845	27	1208	0.97 [0.96, 0.98]	0.15 [0.14, 0.16]



I.2 Dietary interventions

I.2.1 High polyunsaturated fat diet versus usual diet

I.2.1.1 Primary prevention populations

Figure 17: High polyunsaturated fat versus usual diet in primary prevention populations: all-cause mortality

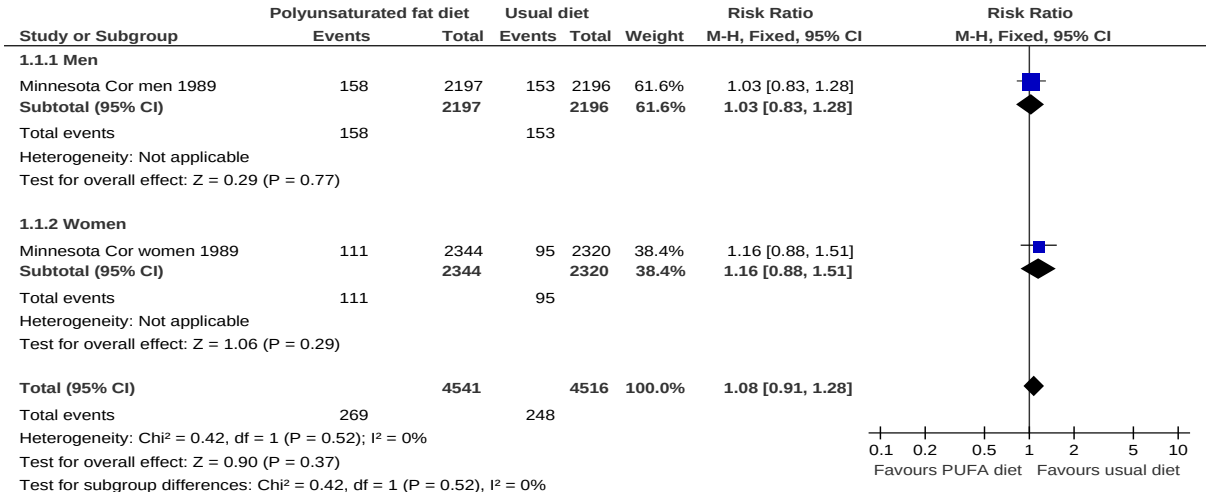
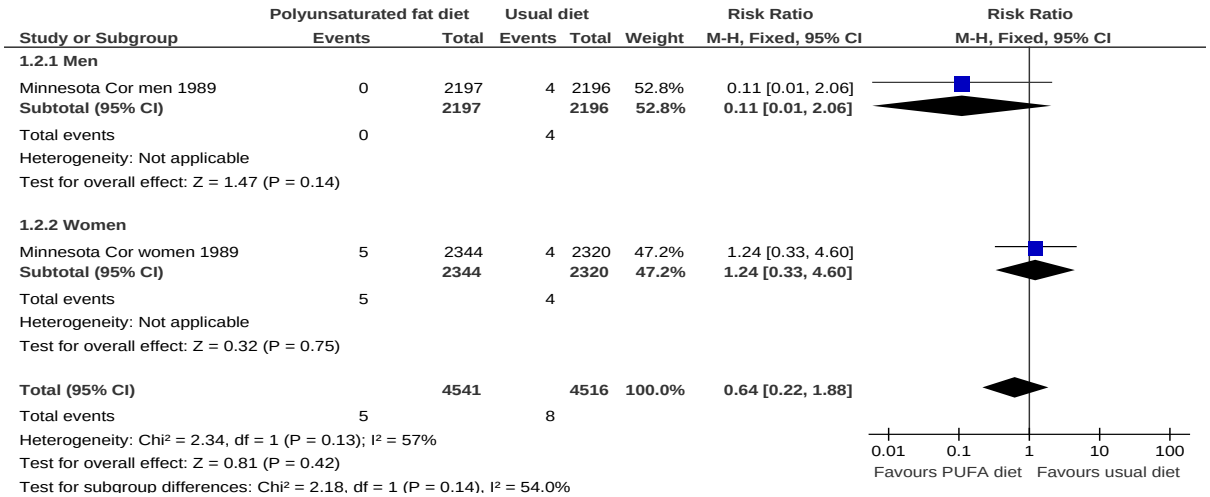


Figure 18: High polyunsaturated fat versus usual diet in primary prevention populations: stroke



I.2.1.2 Primary and secondary prevention populations

Figure 19: High polyunsaturated fat versus usual diet in primary and secondary prevention populations: all-cause mortality

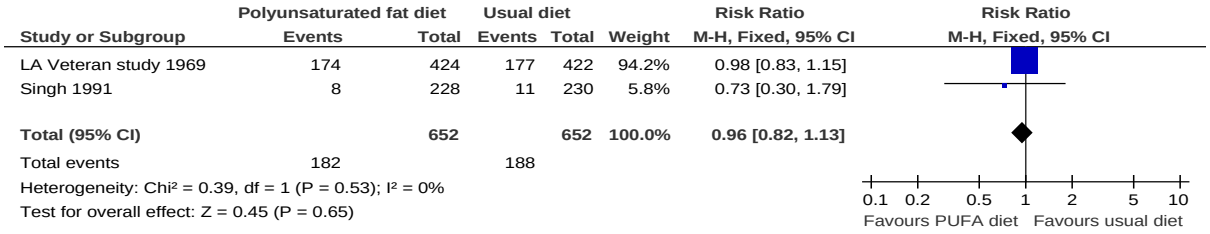


Figure 20: High polyunsaturated fat versus usual diet in primary and secondary prevention populations: CV mortality

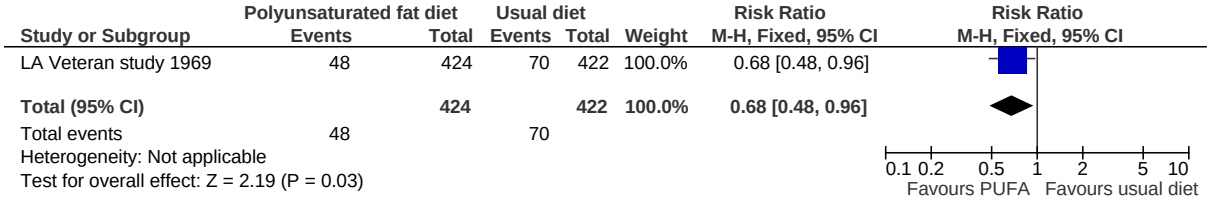


Figure 21: High polyunsaturated fat versus usual diet in primary and secondary prevention populations: non-fatal MI

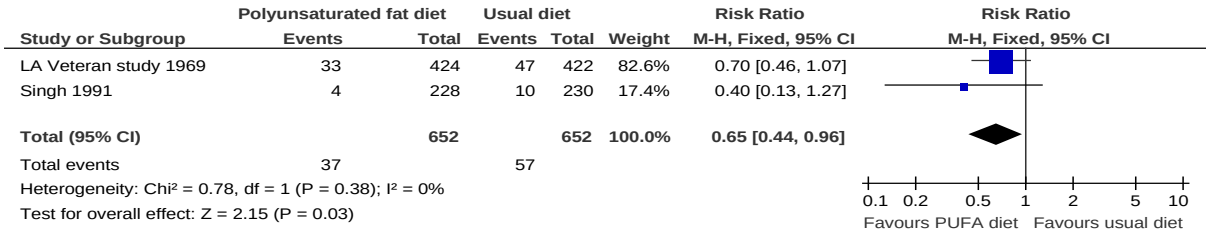
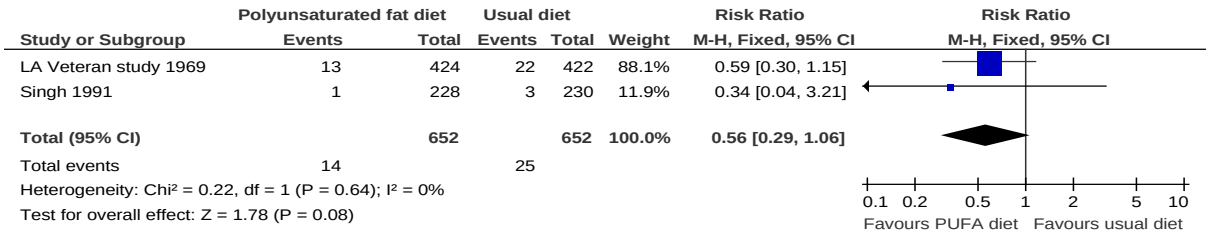


Figure 22: High polyunsaturated fat versus usual diet in primary and secondary prevention populations: stroke



I.2.1.3 Secondary prevention populations

Figure 23: High polyunsaturated fat versus usual diet in secondary prevention populations: all-cause mortality

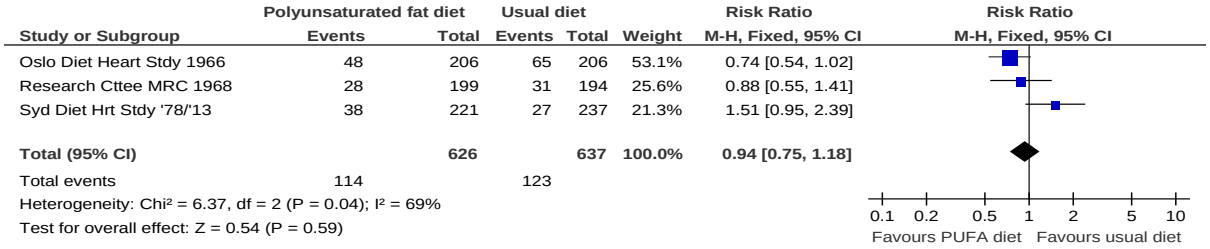


Figure 24: High polyunsaturated fat versus usual diet in secondary prevention populations: CV mortality

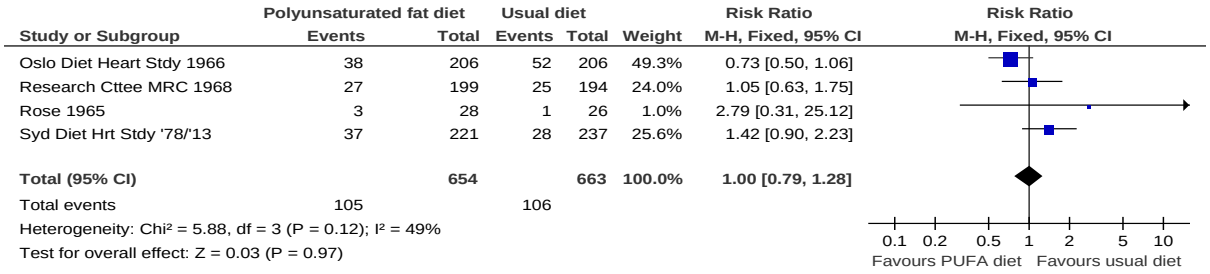


Figure 25: High polyunsaturated fat versus usual diet in secondary prevention populations: non-fatal MI

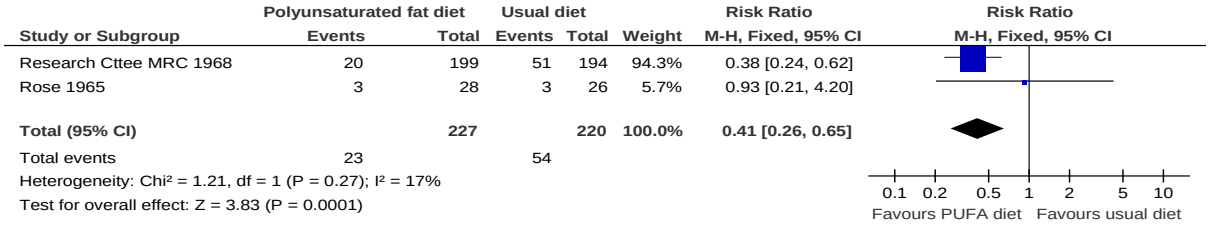


Figure 26: High polyunsaturated fat versus usual diet in secondary prevention populations: all-cause mortality, time-to-event

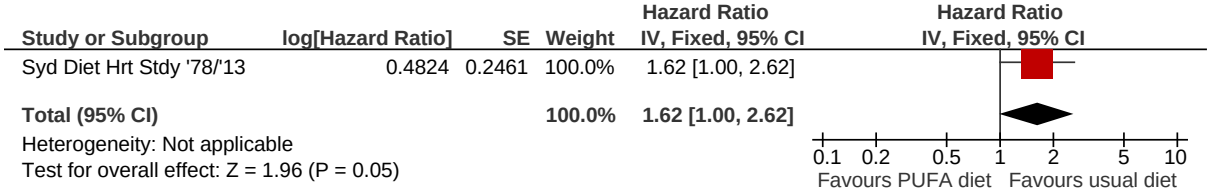
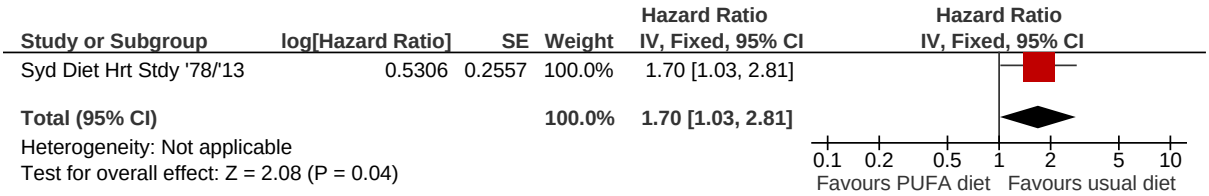


Figure 27: High polyunsaturated fat versus usual diet in secondary prevention populations: CV mortality, time-to-event



I.2.2 Low fat diet versus usual diet

I.2.2.1 Secondary prevention populations

Figure 28: Low fat versus usual diet in secondary prevention populations: all-cause mortality

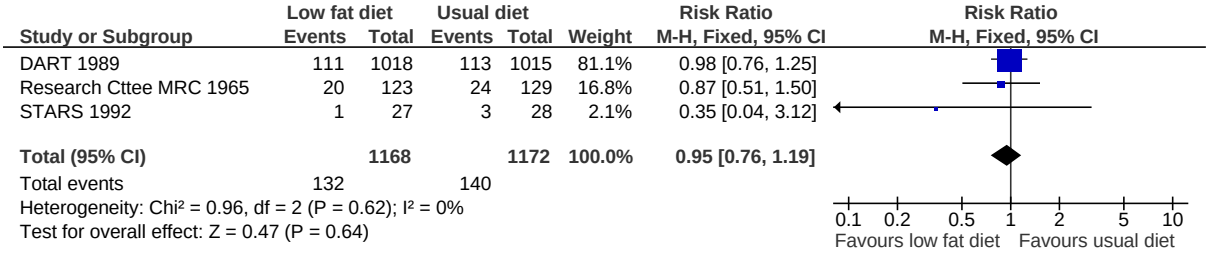


Figure 29: Low fat versus usual diet in secondary prevention populations: CV mortality

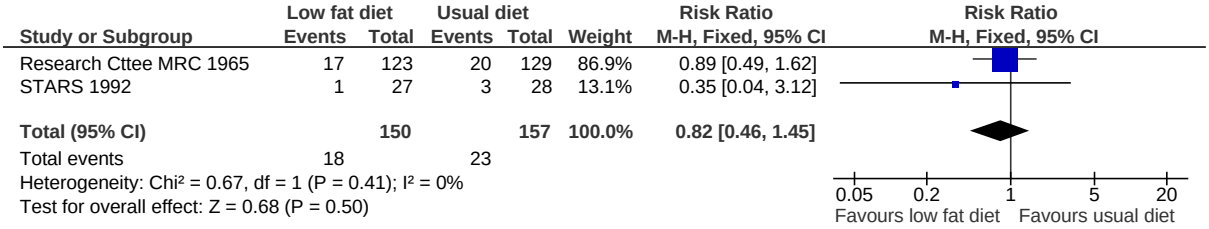


Figure 30: Low fat versus usual diet in secondary prevention populations: non-fatal MI

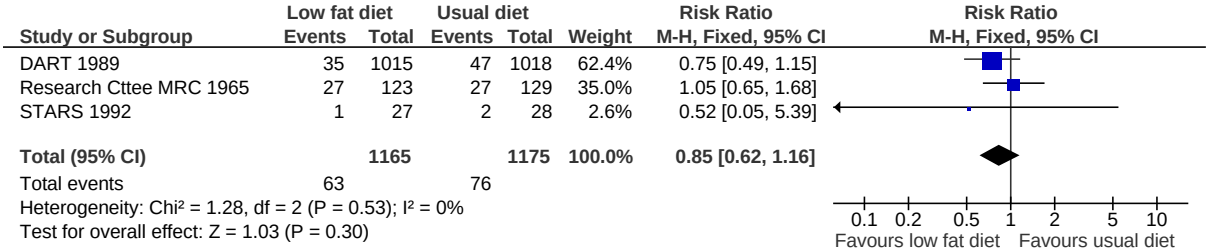
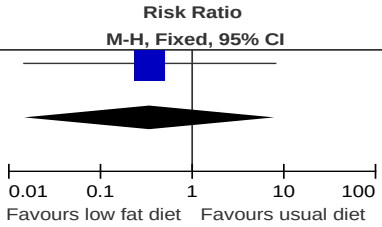


Figure 31: Low fat versus usual diet in secondary prevention populations: stroke

Study or Subgroup	Low fat diet Events	Total	Usual diet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
STARS 1992	0	27	1	28	100.0%	0.35 [0.01, 8.12]
Total (95% CI)		**27**		**28**	**100.0%**	**0.35 [0.01, 8.12]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



I.2.3 Increased fibre diet versus usual diet

I.2.3.1 Secondary prevention populations

Figure 32: Increased fibre versus usual diet in secondary prevention populations: all-cause mortality

Study or Subgroup	Low fibre diet Events	Total	Usual diet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	123	1017	101	1016	100.0%	1.22 [0.95, 1.56]
Total (95% CI)		**1017**		**1016**	**100.0%**	**1.22 [0.95, 1.56]**
Total events	123		101			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

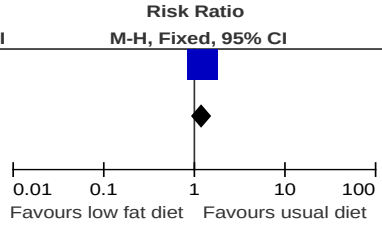
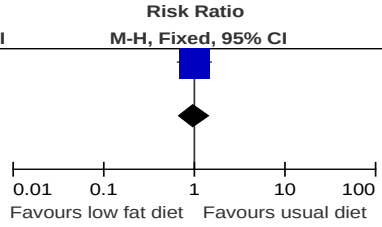


Figure 33: Increased fibre versus usual diet in secondary prevention populations: non-fatal MI

Study or Subgroup	Low fibre diet Events	Total	Usual diet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	41	1017	41	1016	100.0%	1.00 [0.65, 1.53]
Total (95% CI)		**1017**		**1016**	**100.0%**	**1.00 [0.65, 1.53]**
Total events	41		41			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



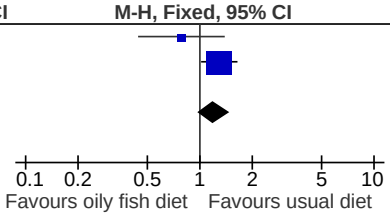
I.2.4 Increased oily fish diet versus usual diet

I.2.4.1 Secondary prevention populations

Figure 34: Increased oily fish versus usual diet in secondary prevention populations: all-cause mortality

Study or Subgroup	Oily fish diet Events	Total	Usual diet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DART 1989	20	257	25	252	18.8%	0.78 [0.45, 1.38]
DART 2 2003	141	764	109	764	81.2%	1.29 [1.03, 1.63]
Total (95% CI)		**1021**		**1016**	**100.0%**	**1.20 [0.97, 1.48]**
Total events	161		134			

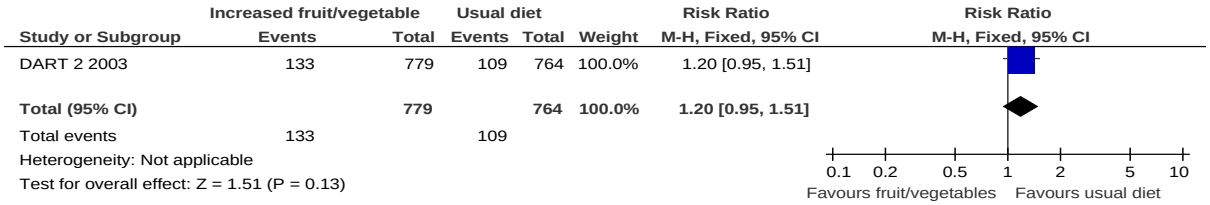
Heterogeneity: Chi² = 2.61, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 1.67 (P = 0.09)



I.2.5 Increased fruit and vegetable diet versus usual diet

I.2.5.1 Secondary prevention populations

Figure 35: Increased fruit and vegetables versus usual diet in secondary prevention populations: all-cause mortality



I.2.6 Mediterranean diet versus usual diet

I.2.6.1 Primary prevention populations

Figure 36: Mediterranean diet versus usual diet in primary prevention populations: all-cause mortality

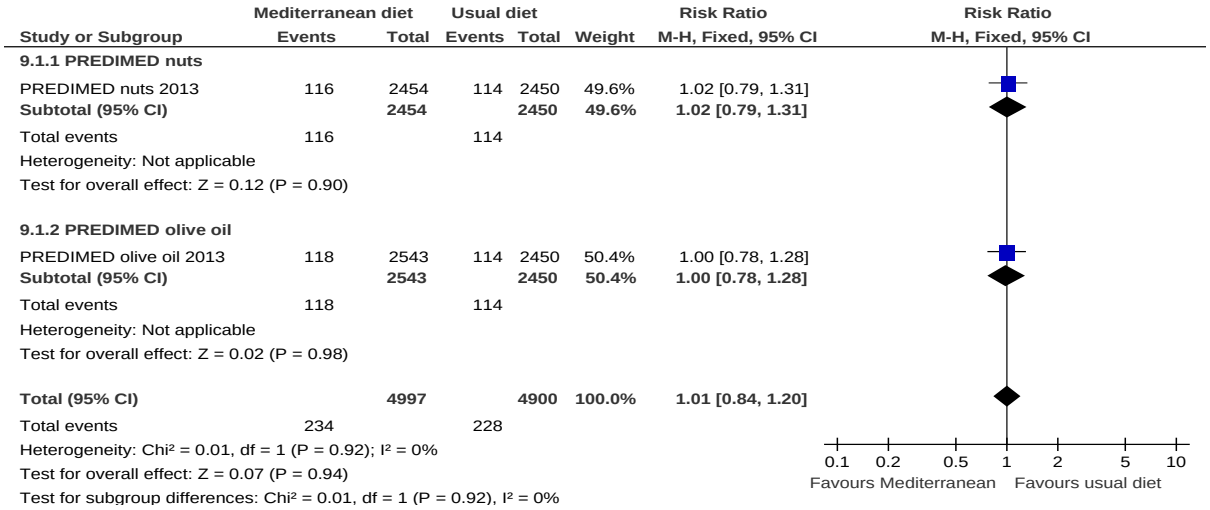


Figure 37: Mediterranean diet versus usual diet in primary populations: CV mortality

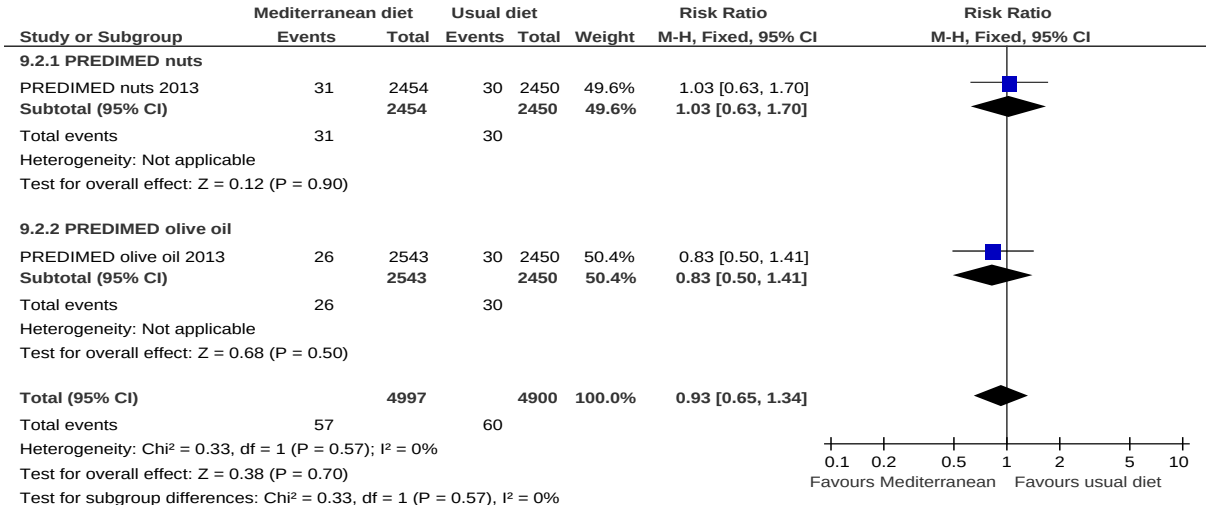


Figure 38: Mediterranean diet versus usual diet in primary populations: non-fatal MI

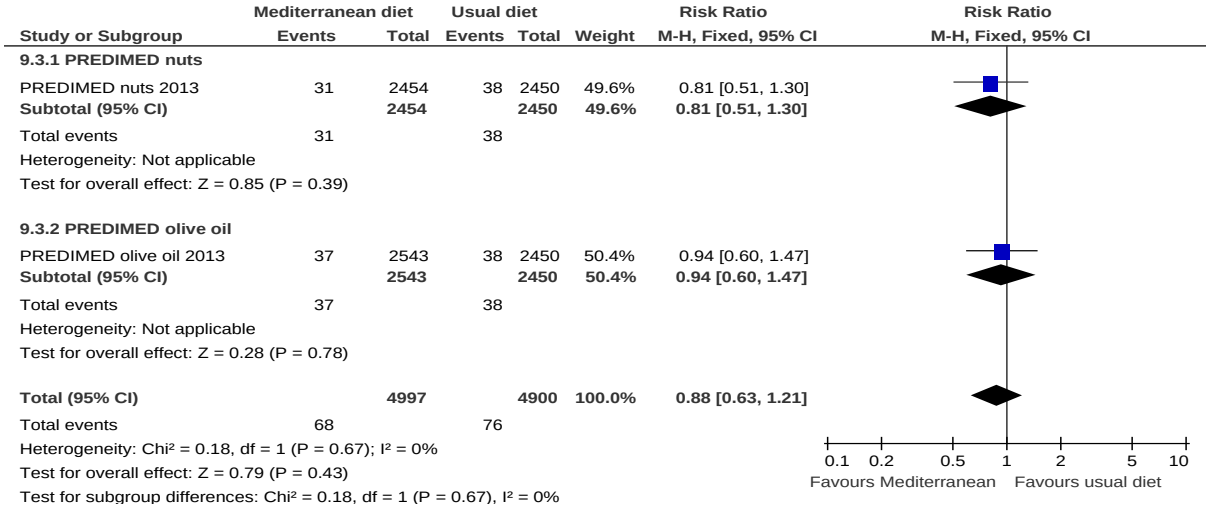


Figure 39: Mediterranean diet versus usual diet in primary populations: stroke

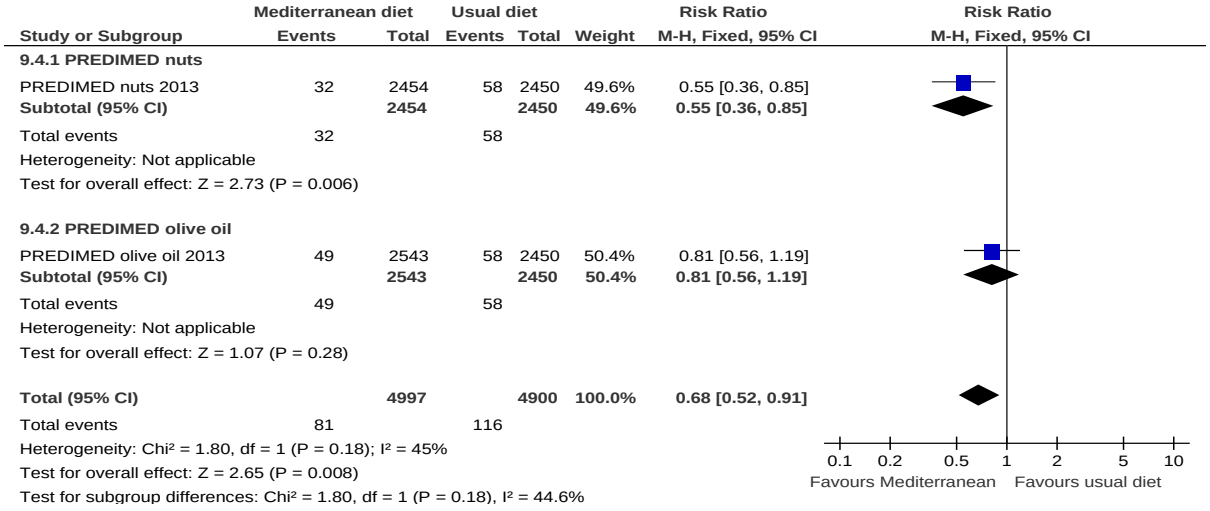


Figure 40: Mediterranean diet versus usual diet in primary prevention populations: all-cause mortality, time-to-event

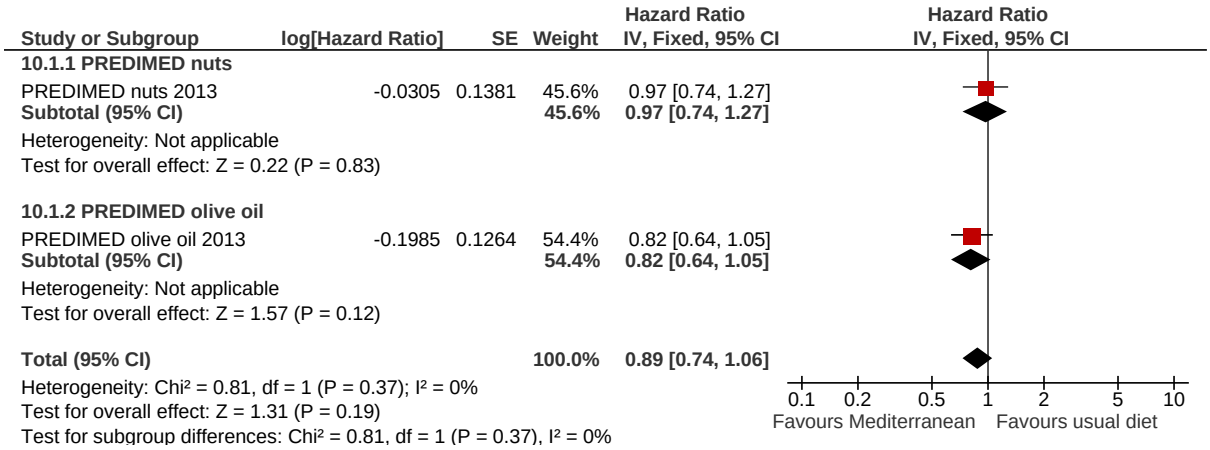


Figure 41: Mediterranean diet versus usual diet in primary populations: CV mortality, time-to-event

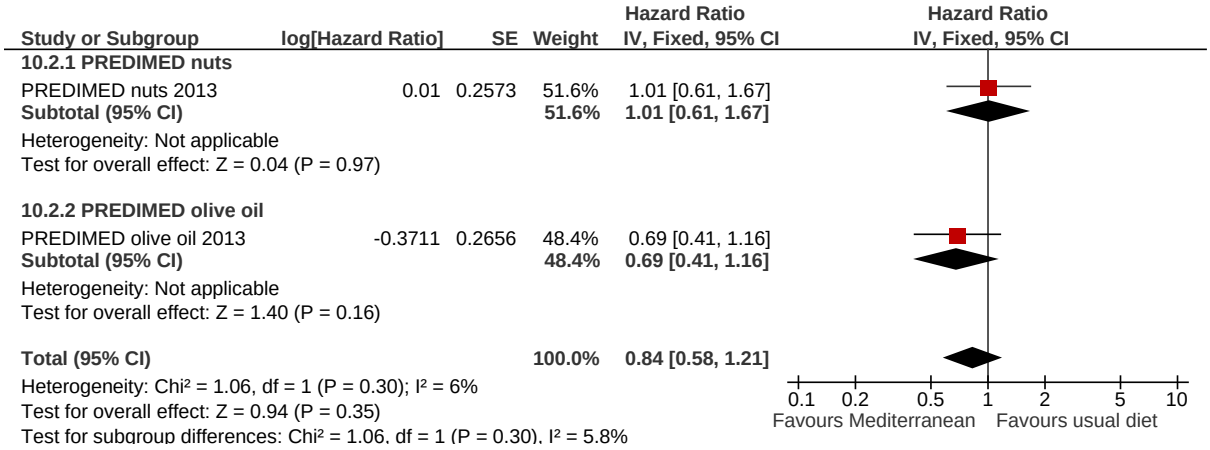


Figure 42: Mediterranean diet versus usual diet in primary populations: non-fatal MI, time-to-event

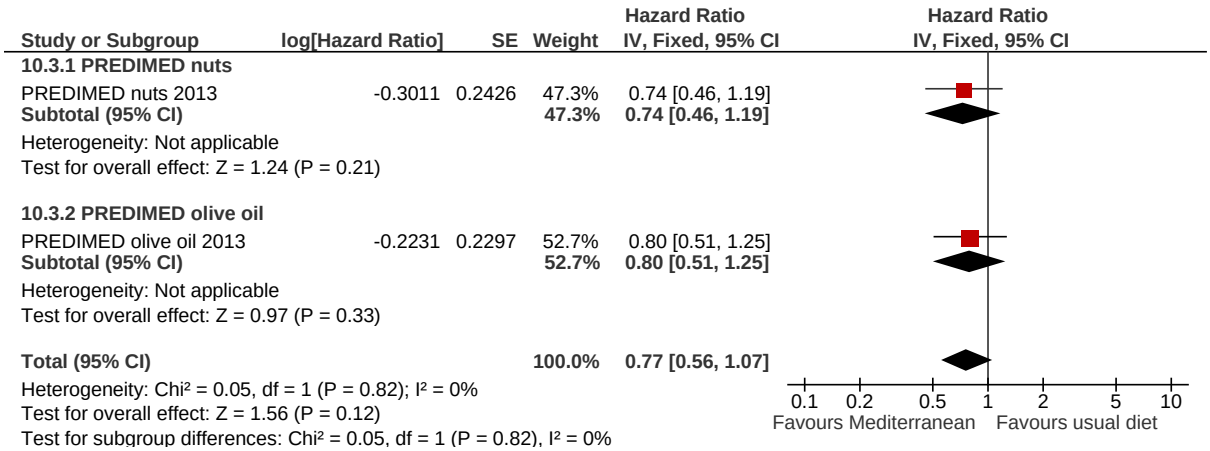
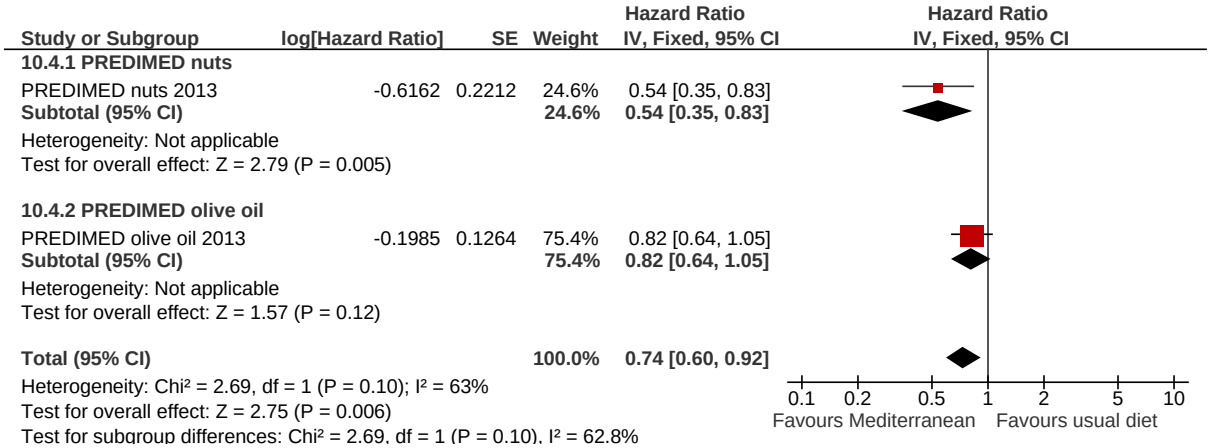


Figure 43: Mediterranean diet versus usual diet in primary populations: stroke, time-to-event



I.2.6.2 Primary and secondary prevention populations

Figure 44: Mediterranean diet versus usual diet in primary and secondary populations: all-cause mortality

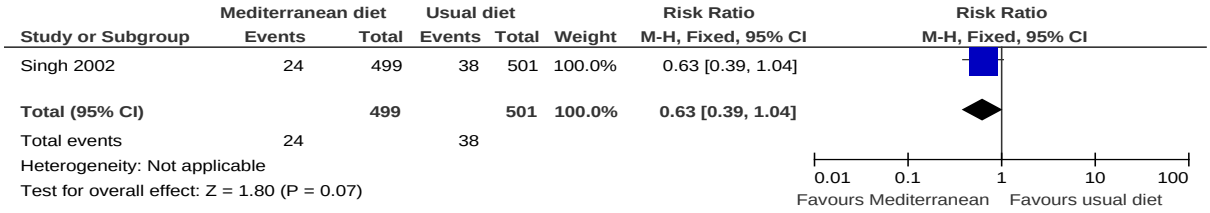


Figure 45: Mediterranean diet versus usual diet in primary and secondary populations: non-fatal MI

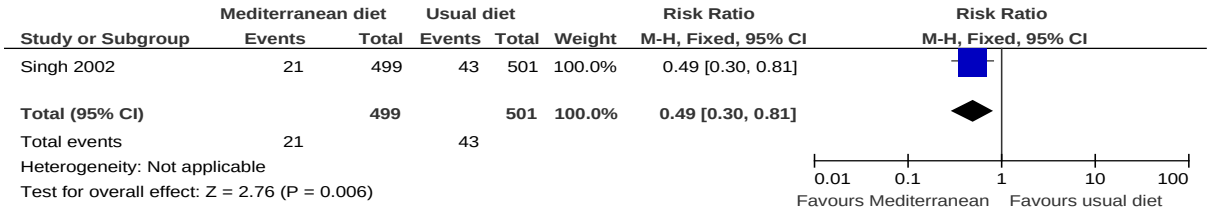
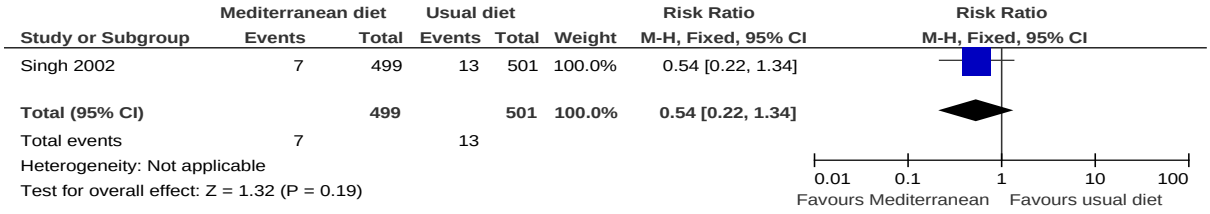


Figure 46: Mediterranean diet versus usual diet in primary and secondary populations: stroke



I.2.6.3 Secondary prevention populations

Figure 47: Mediterranean diet versus usual diet in secondary populations: all-cause mortality

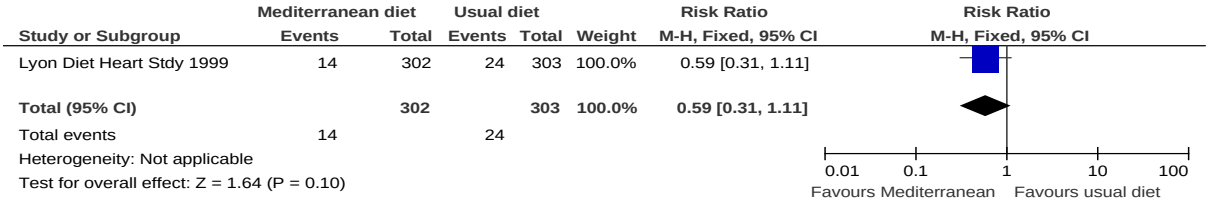


Figure 48: Mediterranean diet versus usual diet in secondary populations: non-fatal MI

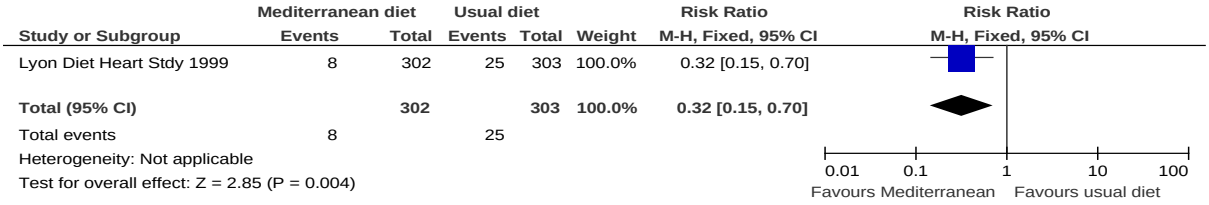
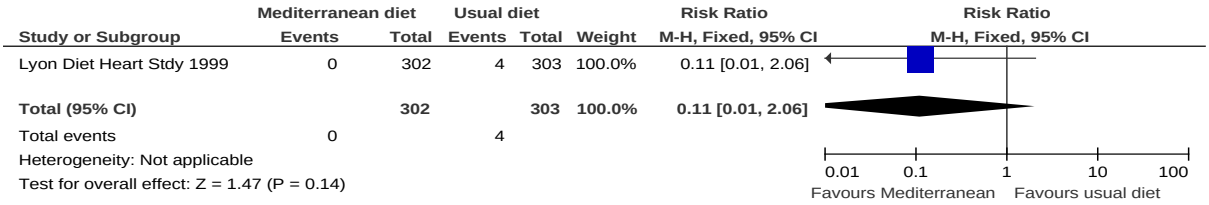


Figure 49: Mediterranean diet versus usual diet in secondary populations: stroke



I.3 Foods enriched with phytosterols (plant stanols and sterols)

None

I.4 Efficacy of statin therapy

I.4.1 Statins versus placebo: subgroup analysis by statin intensity

Figure 50: All-cause mortality (subgroup analysis by statin intensity)

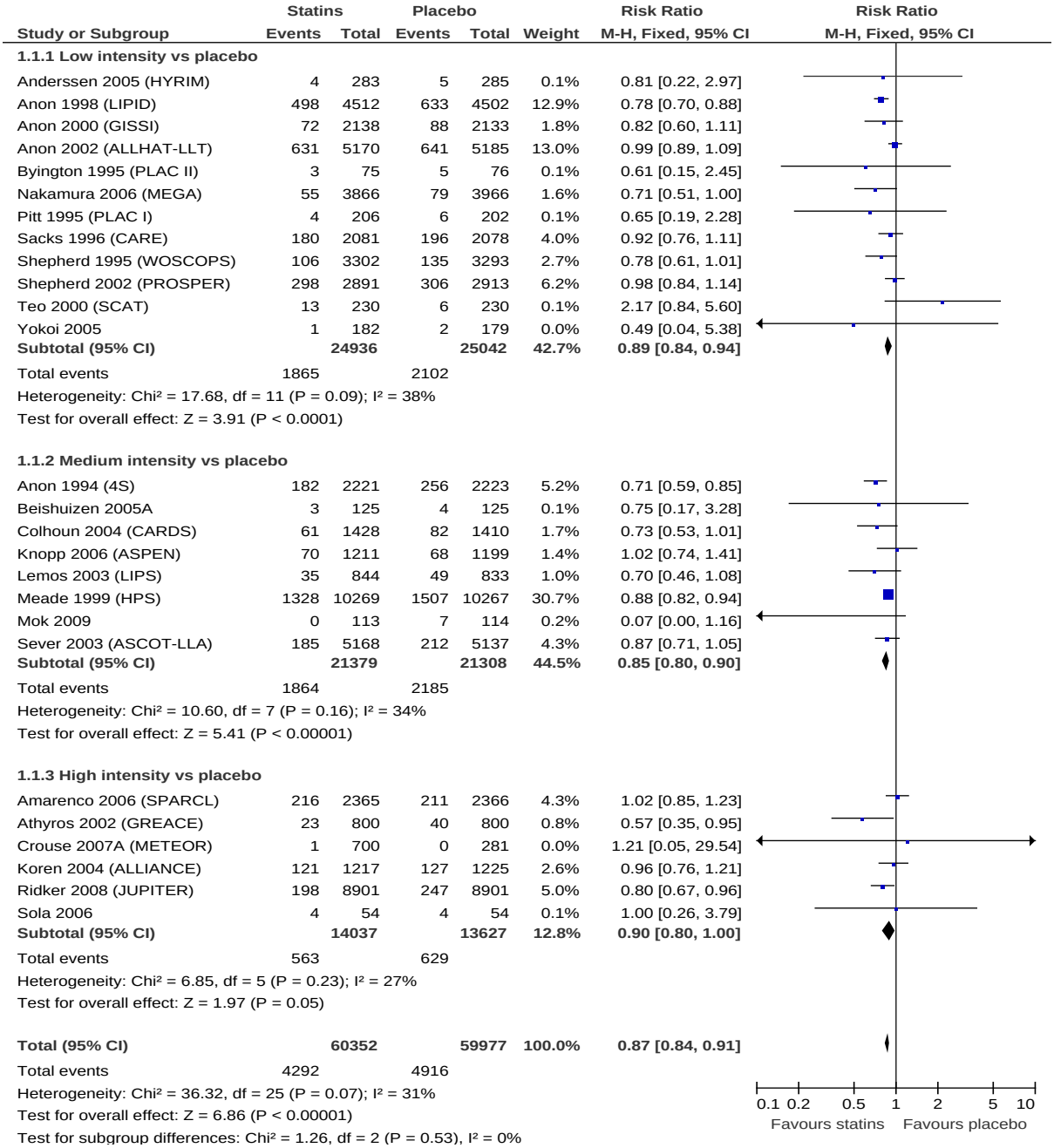


Figure 51: CV mortality (subgroup analysis by statin intensity)

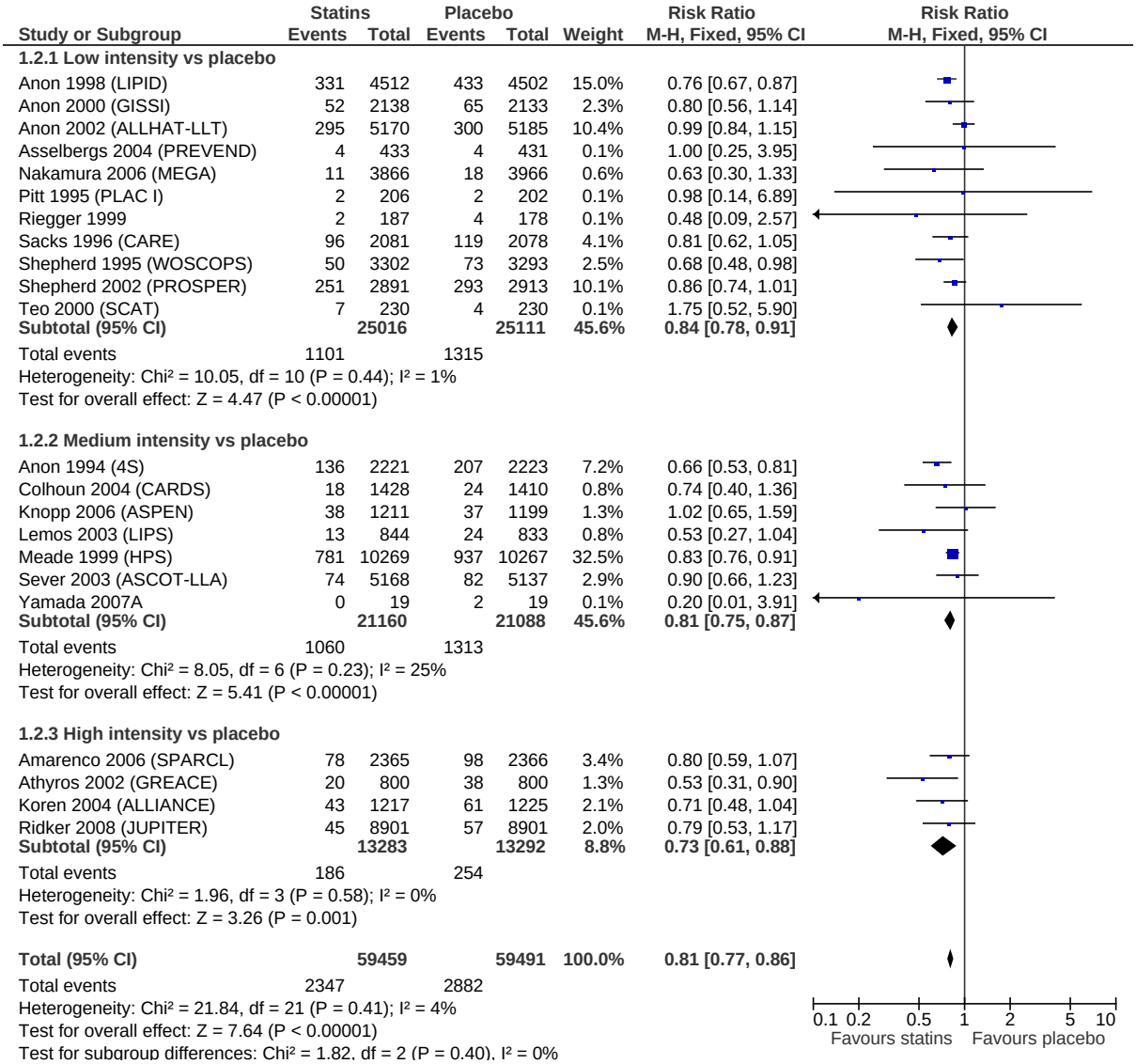


Figure 52: Non-fatal MI (subgroup analysis by statin intensity)

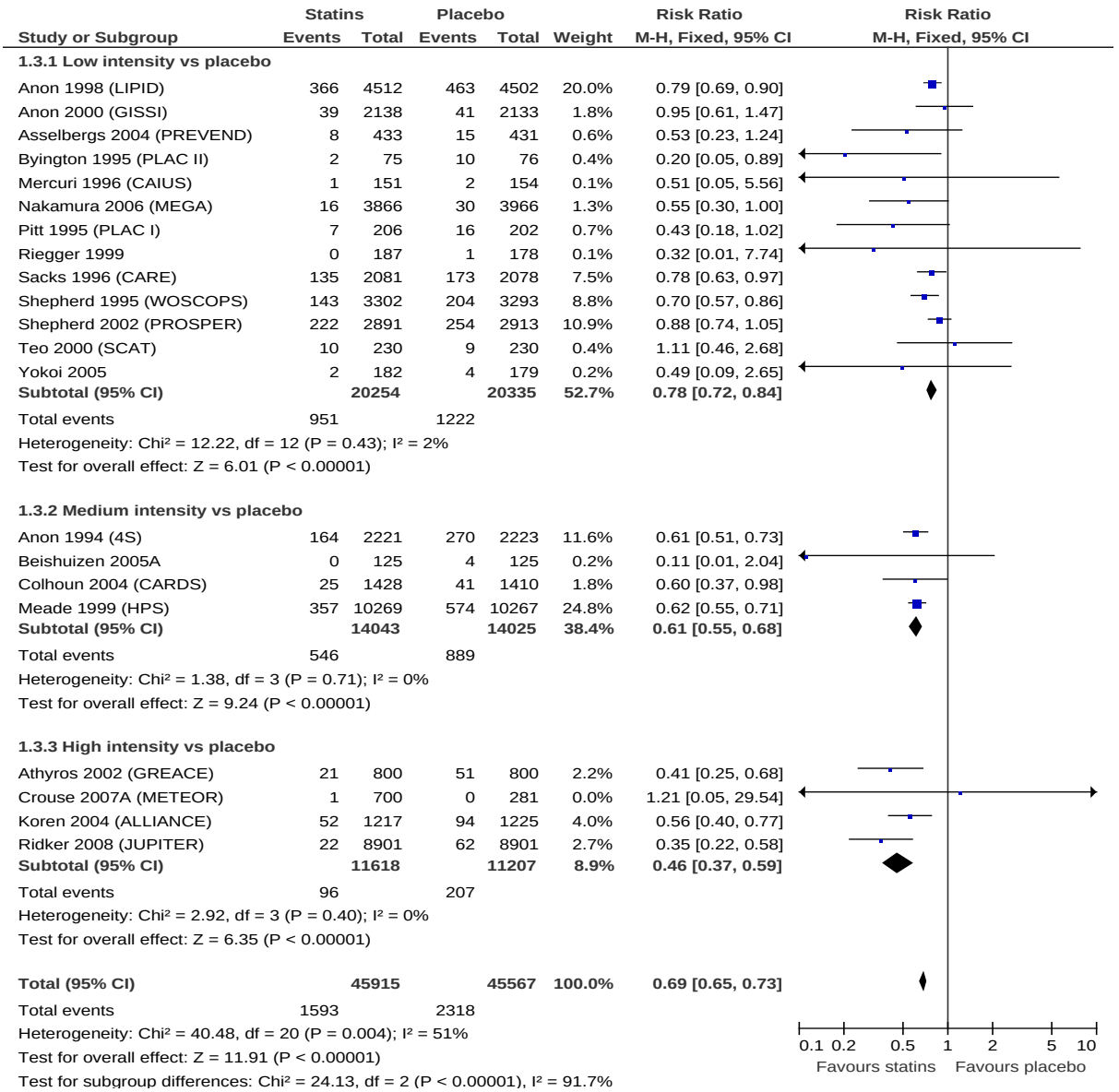


Figure 53: Stroke (subgroup analysis by statin intensity)

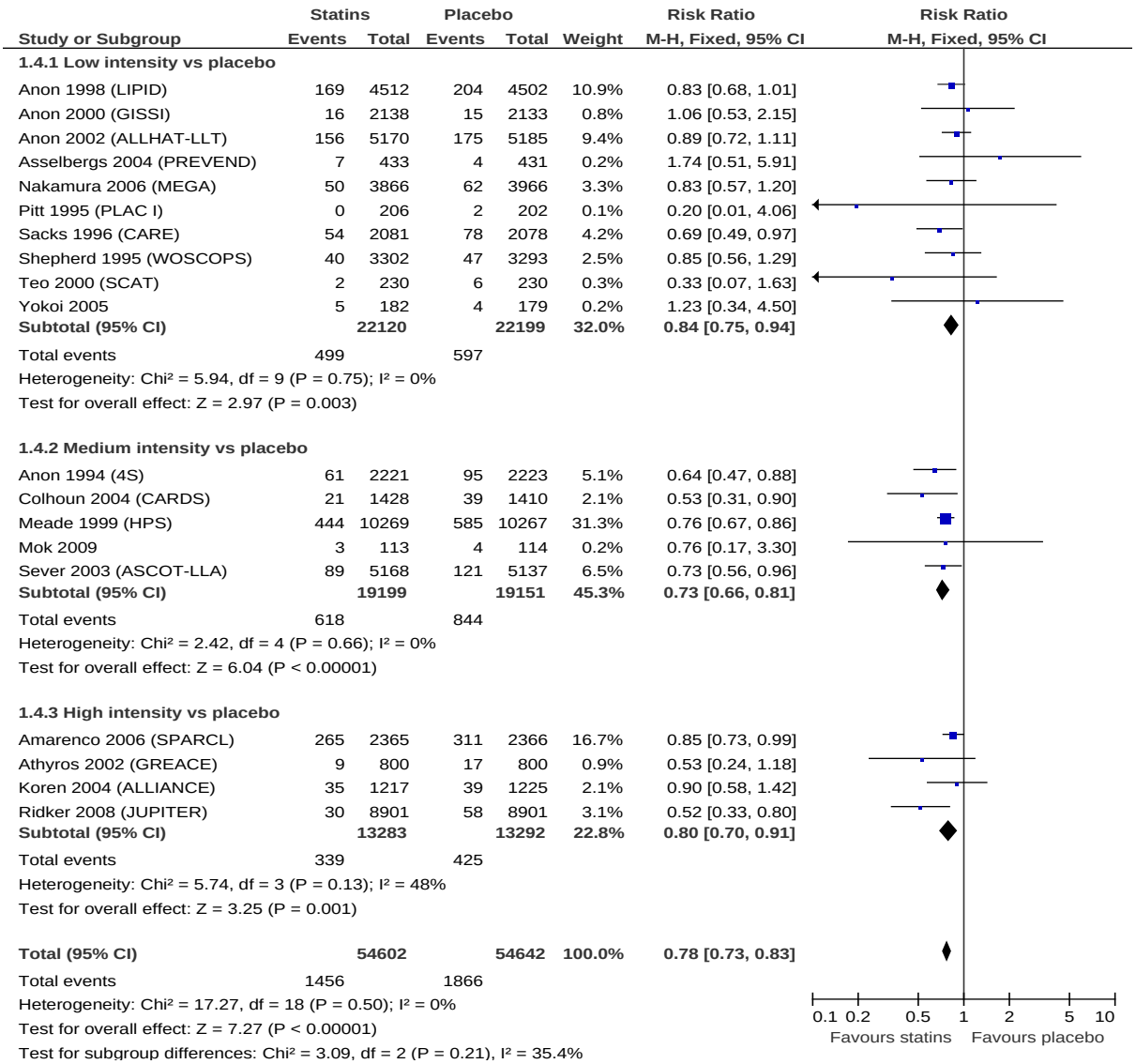


Figure 54: Adverse events: myalgia (subgroup analysis by statin intensity)

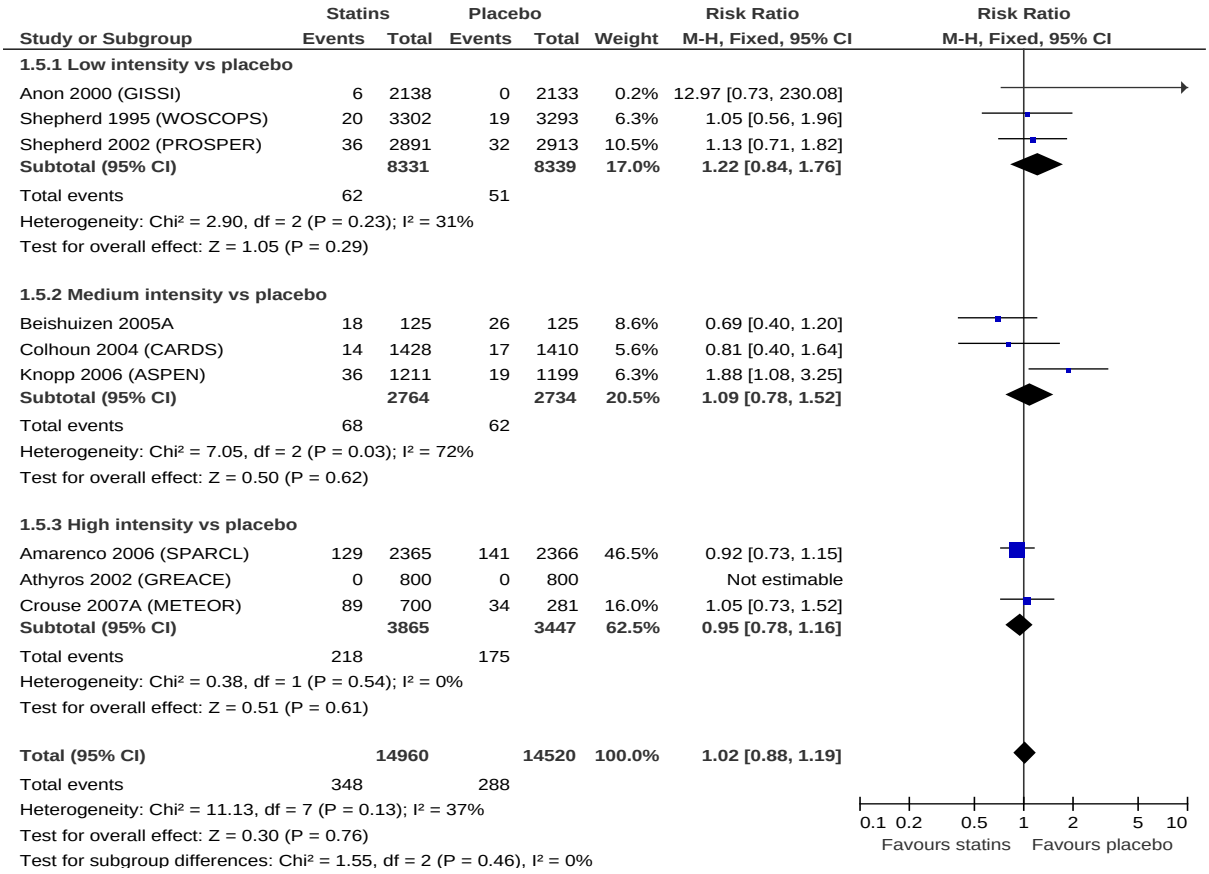


Figure 55: Adverse events: liver adverse events (transaminases >3 x ULN) (subgroup analysis by statin intensity)

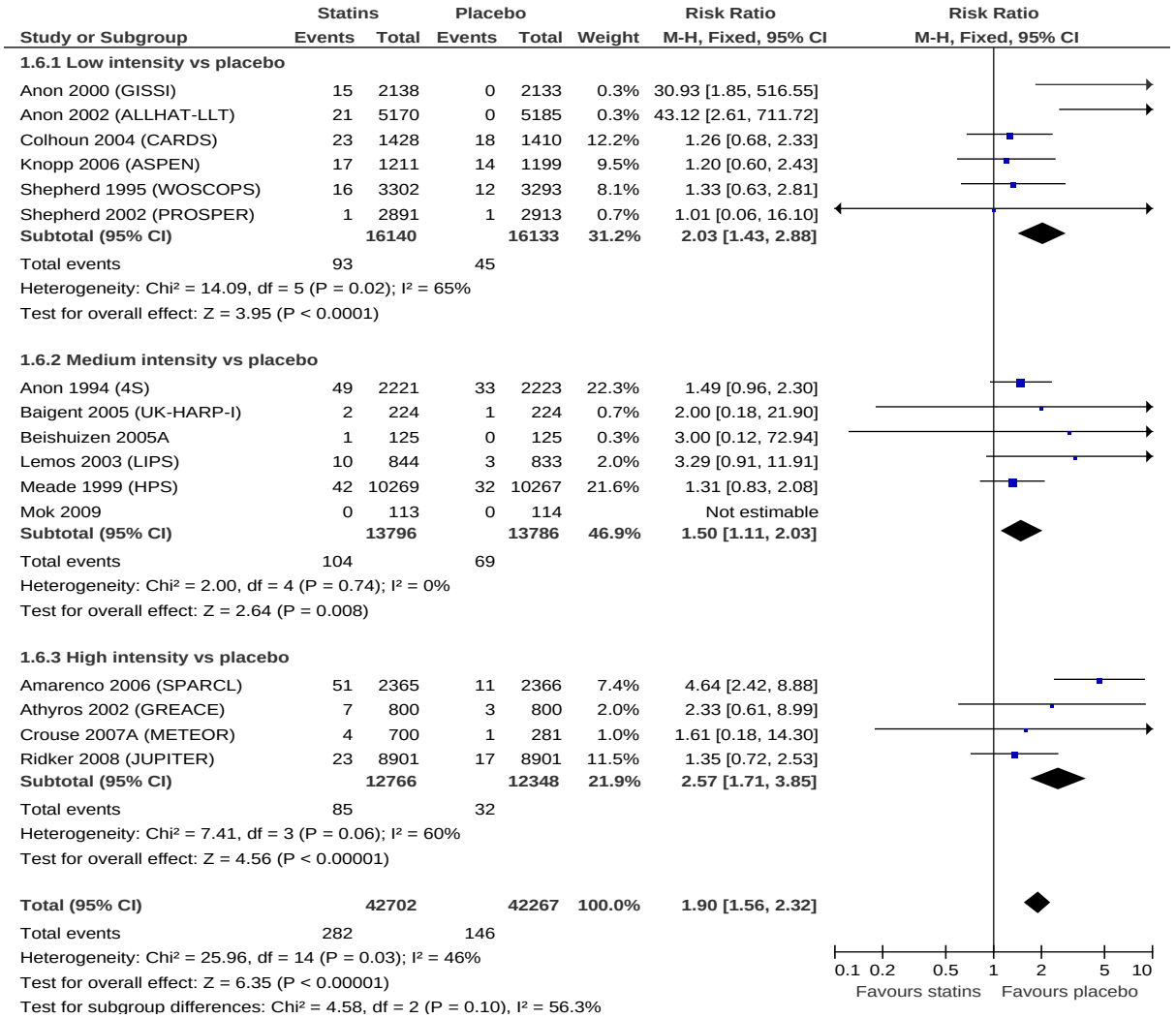


Figure 56: Adverse event: new-onset diabetes (subgroup analysis by statin intensity)

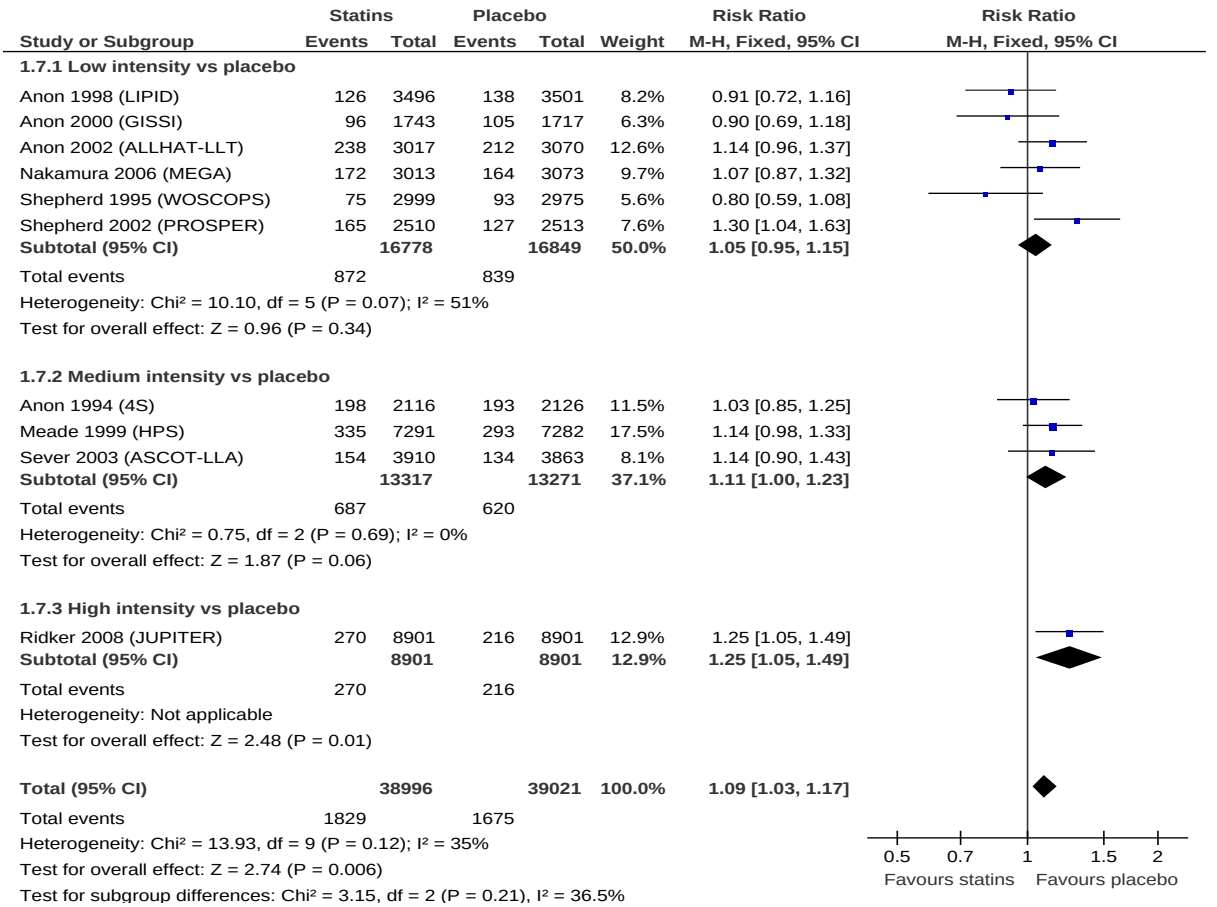


Figure 57: Adverse event: rhabdomyolysis (subgroup analysis by statin intensity)

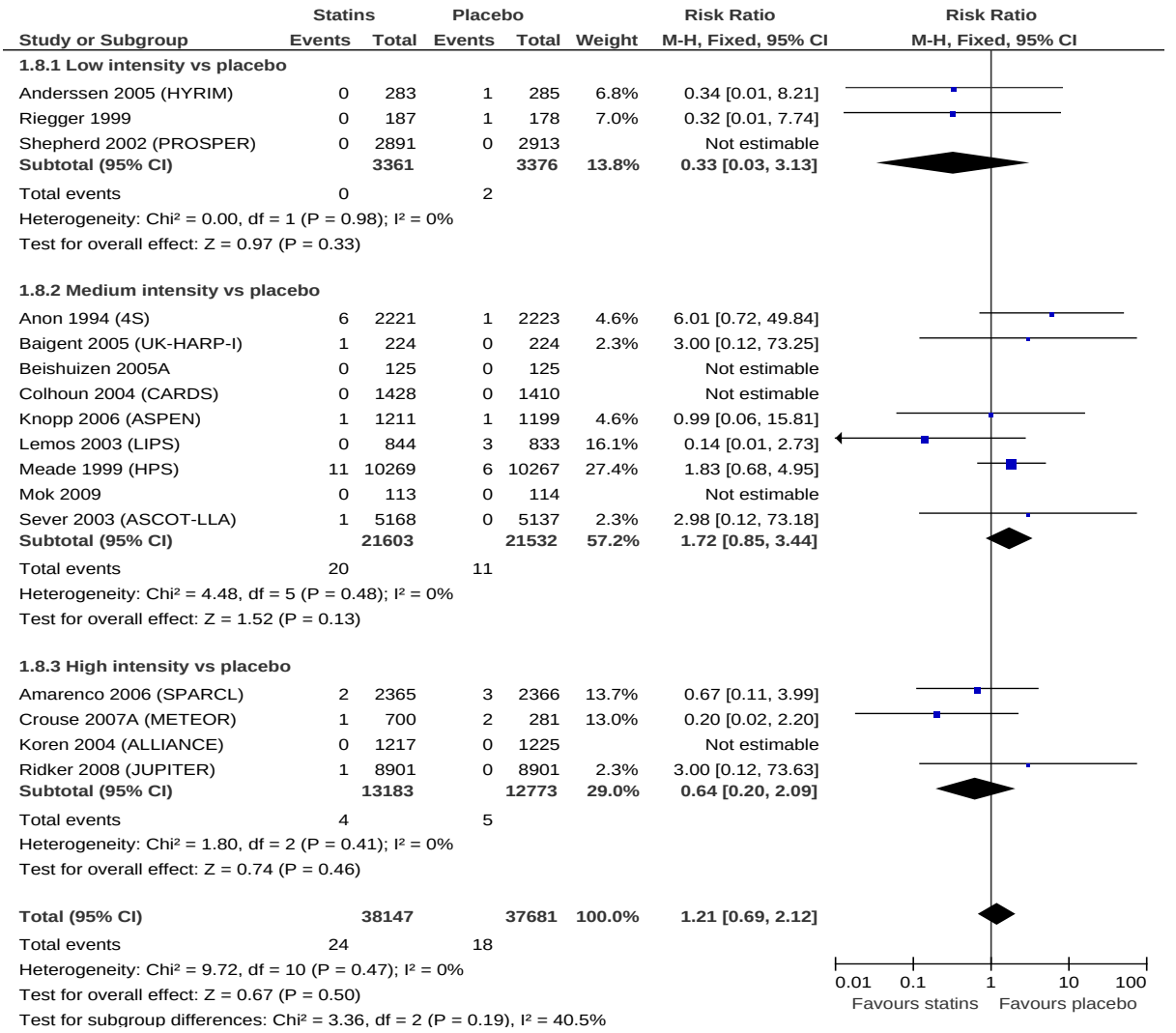
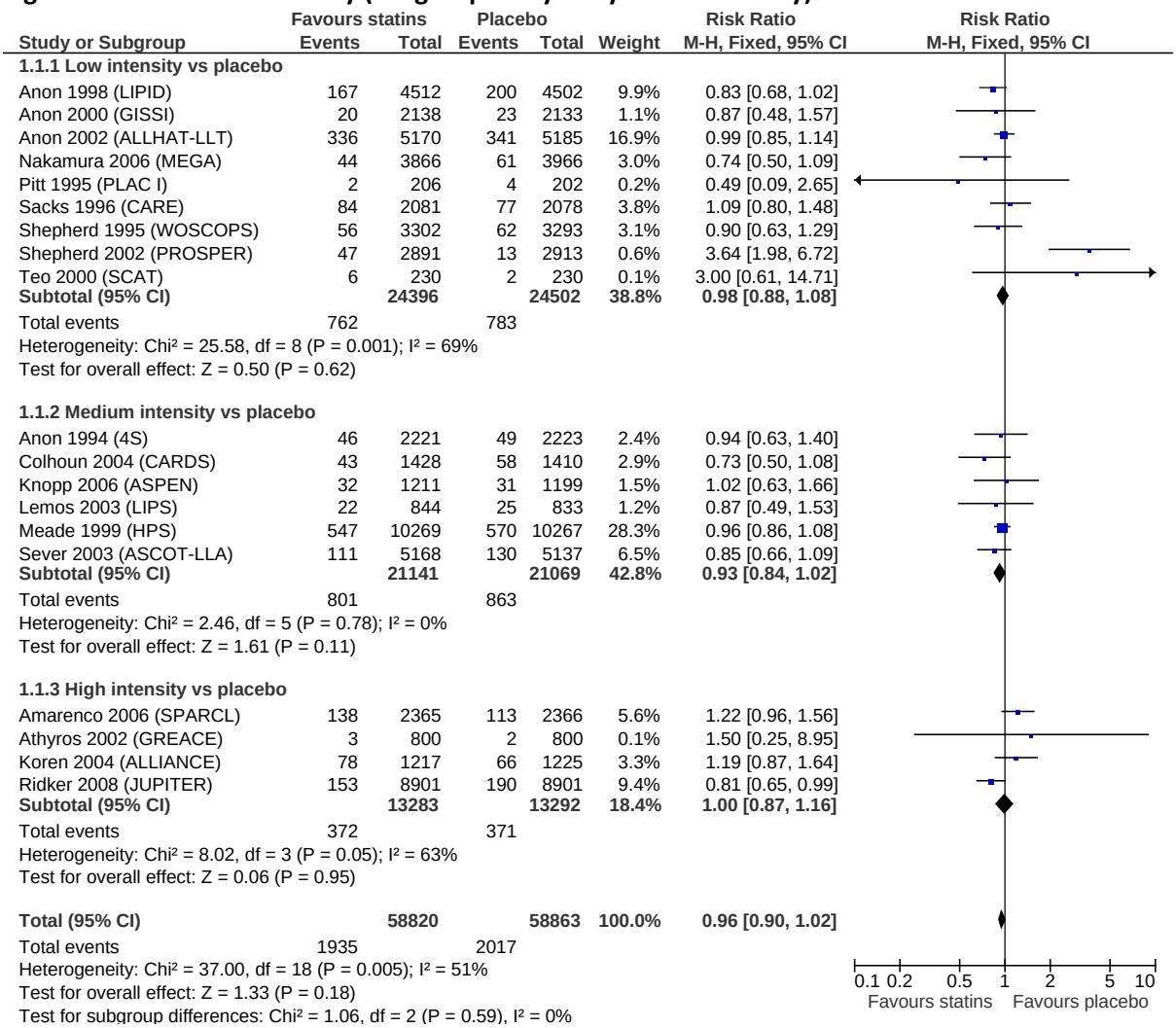


Figure 58: Non-CVD mortality (subgroup analysis by statin intensity)



I.4.2 Statins versus placebo: subgroup analysis by strata

Figure 59: All-cause mortality (subgroup analysis by strata)

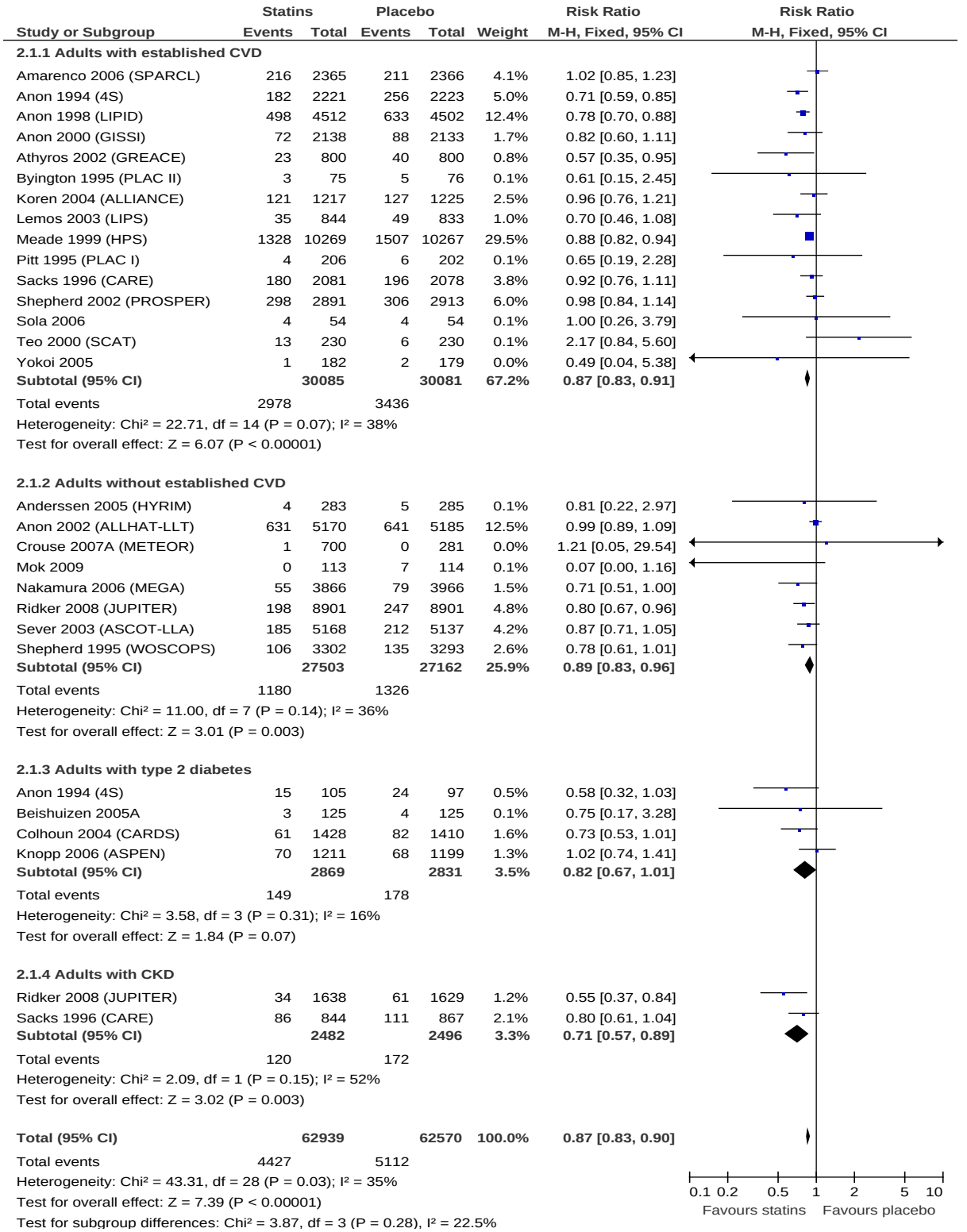


Figure 60: CV mortality (subgroup analysis by strata)

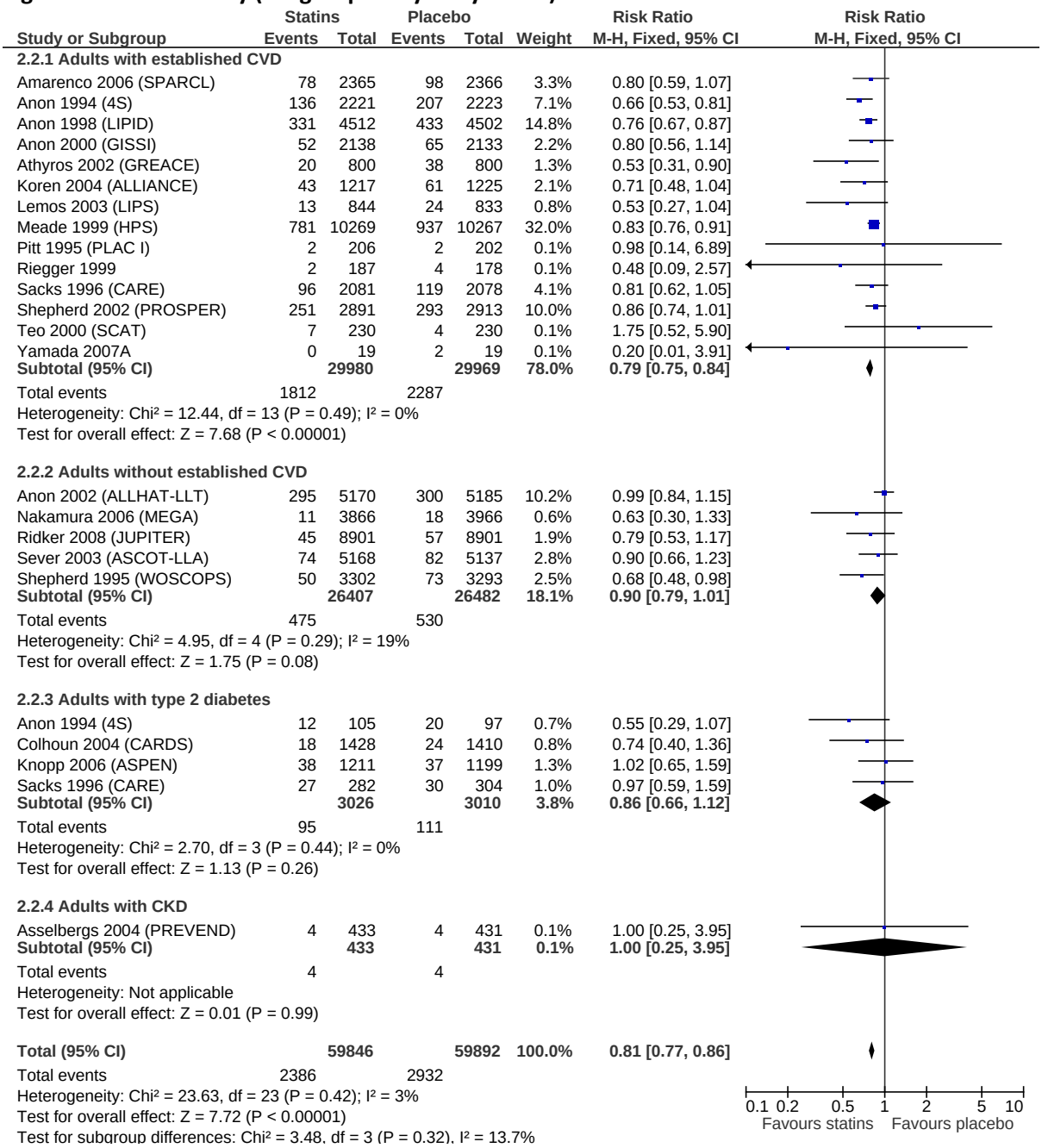


Figure 61: Non-fatal MI (subgroup analysis by strata)

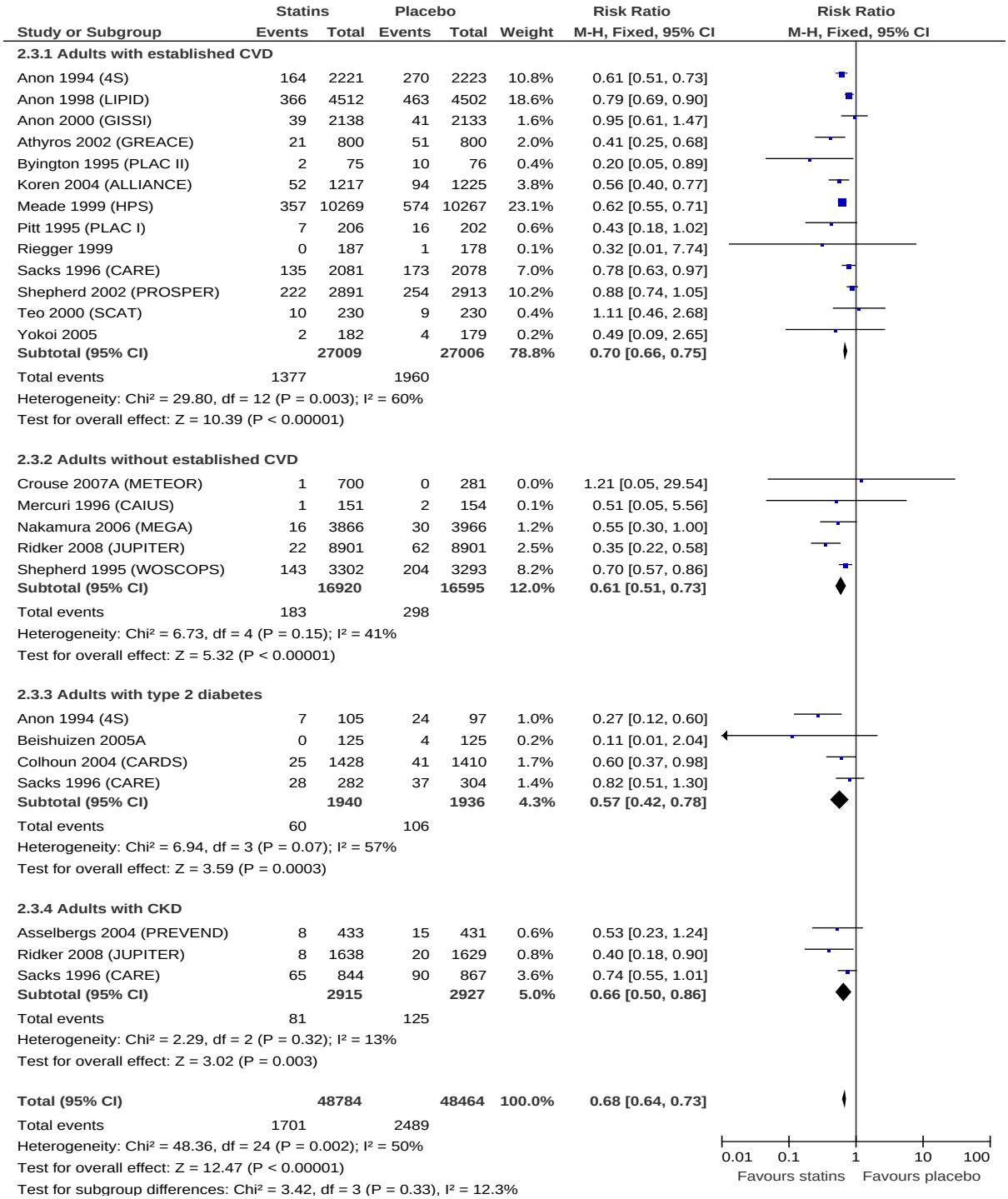


Figure 62: Stroke (subgroup analysis by strata)

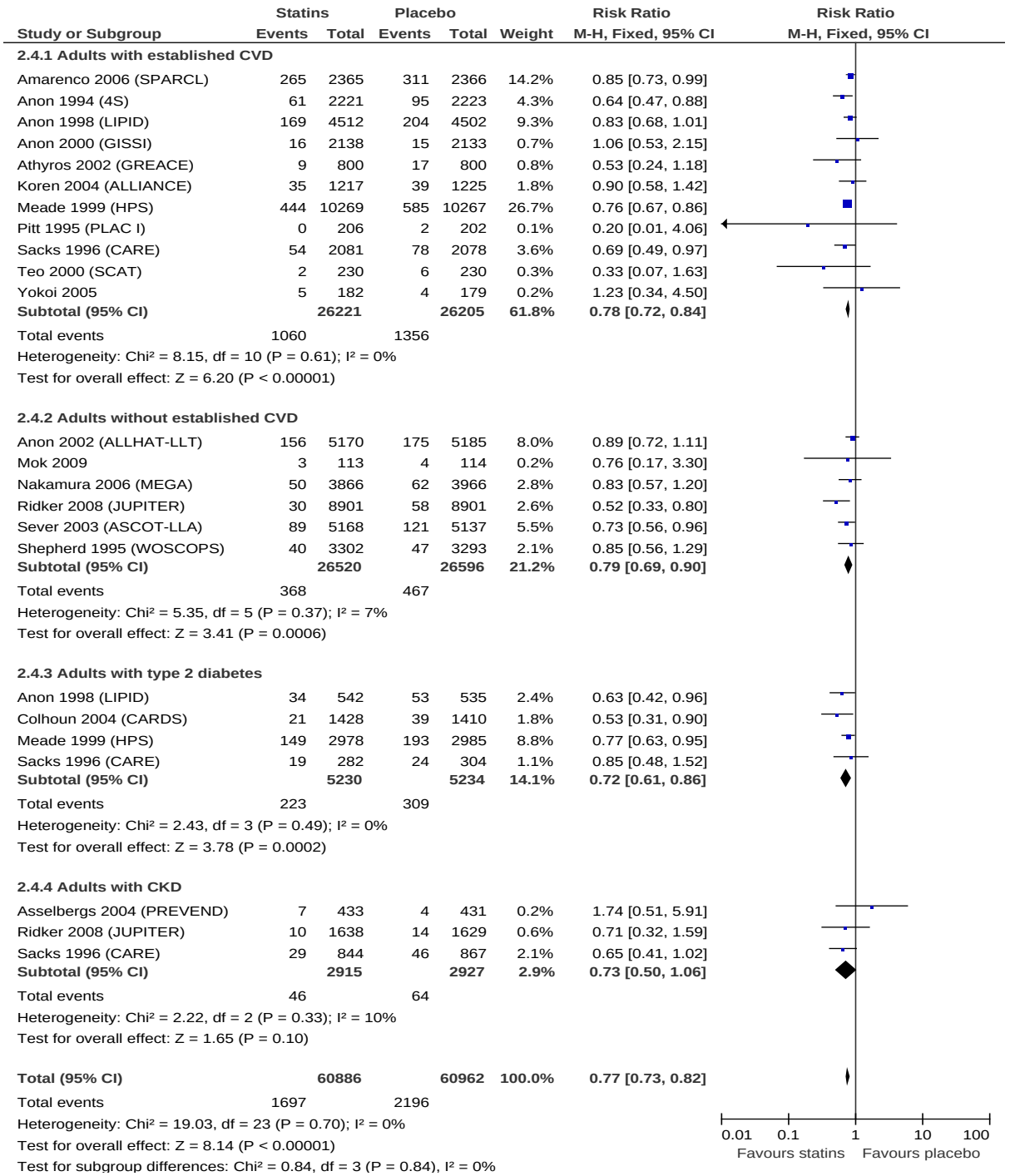


Figure 63: Adverse events: myalgia (subgroup analysis by strata)

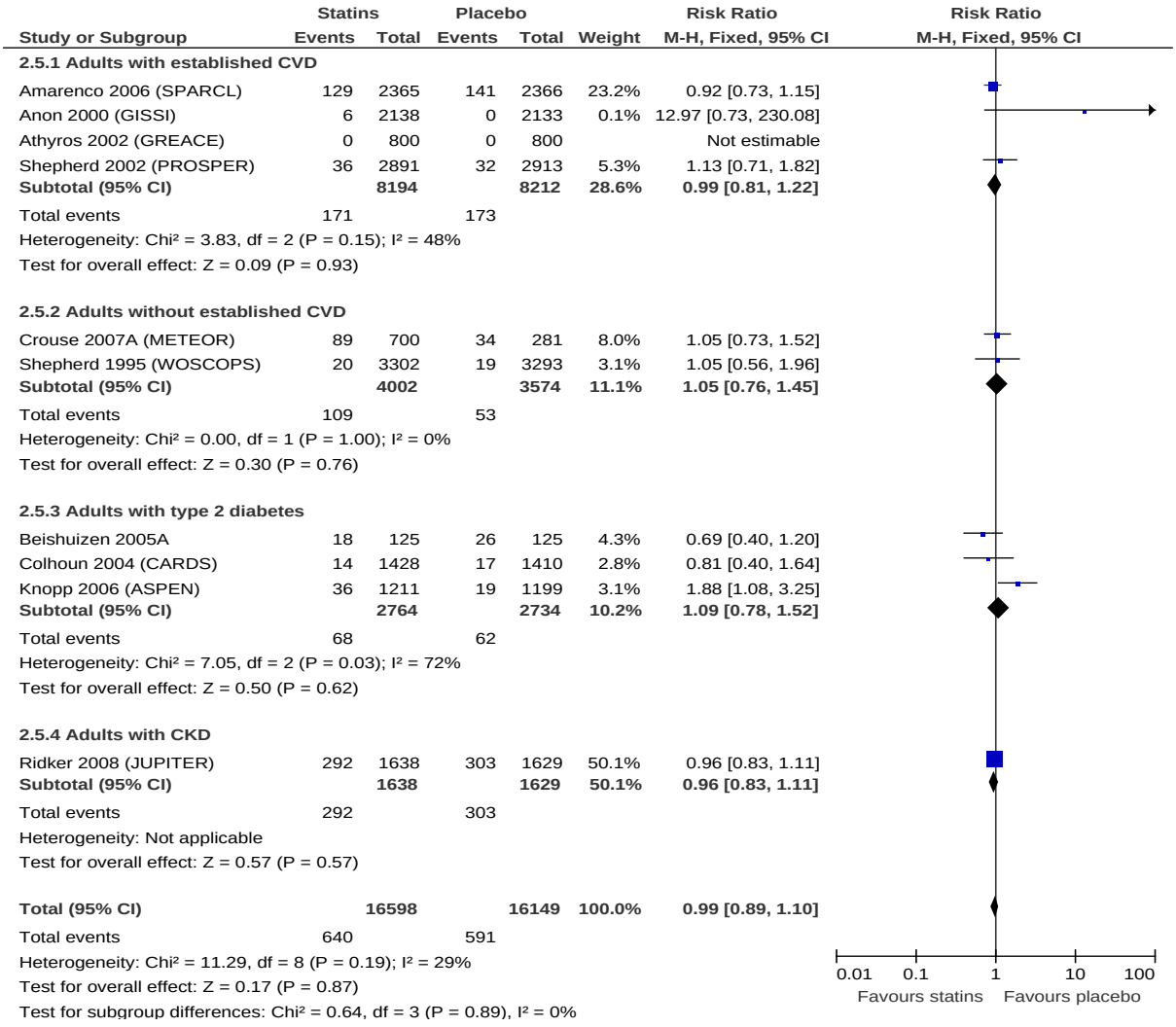


Figure 64: Adverse events: liver adverse events (transaminases >3 x ULN) (subgroup analysis by strata)

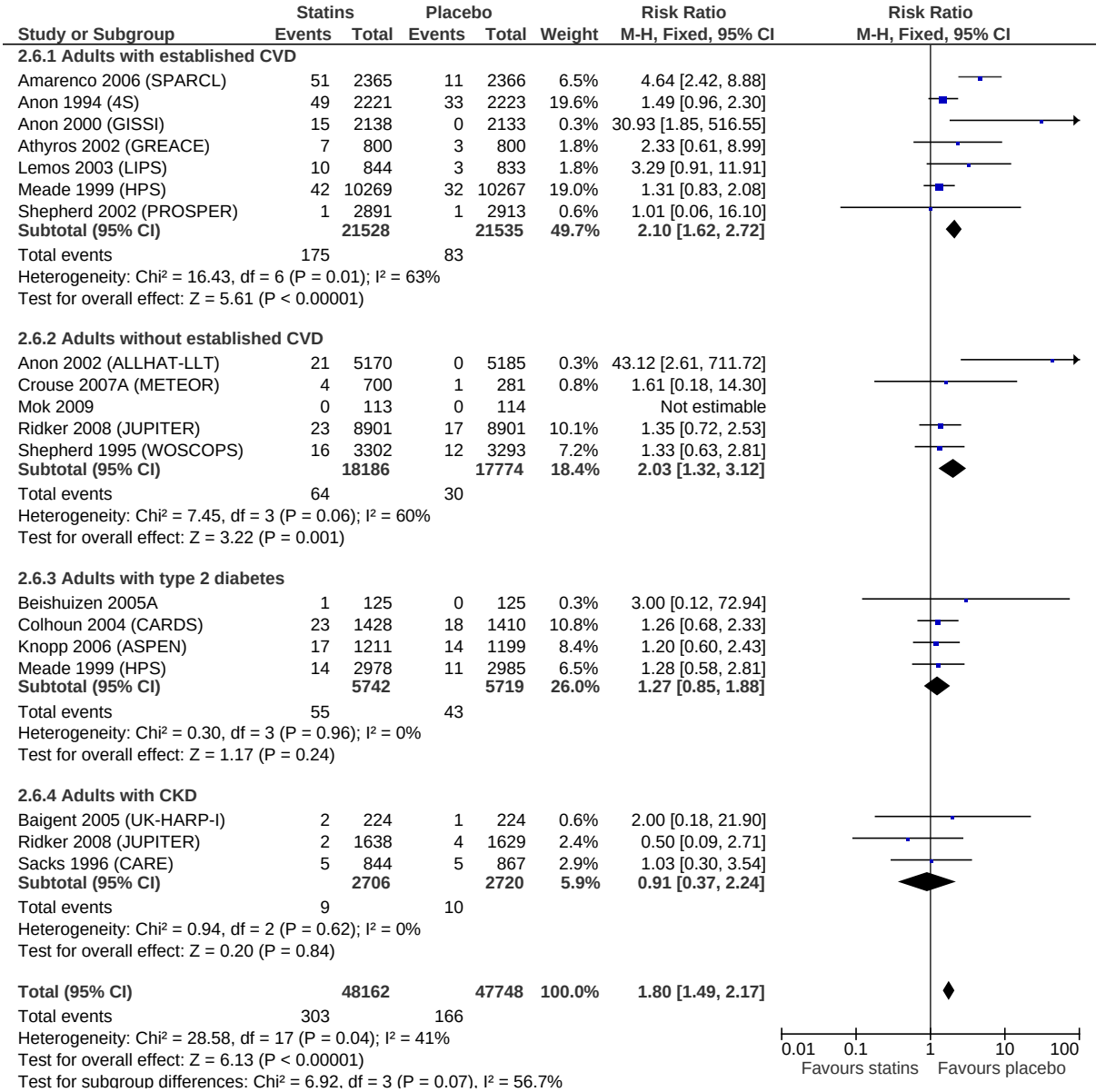


Figure 65: Adverse events: new-onset diabetes (subgroup analysis by strata)

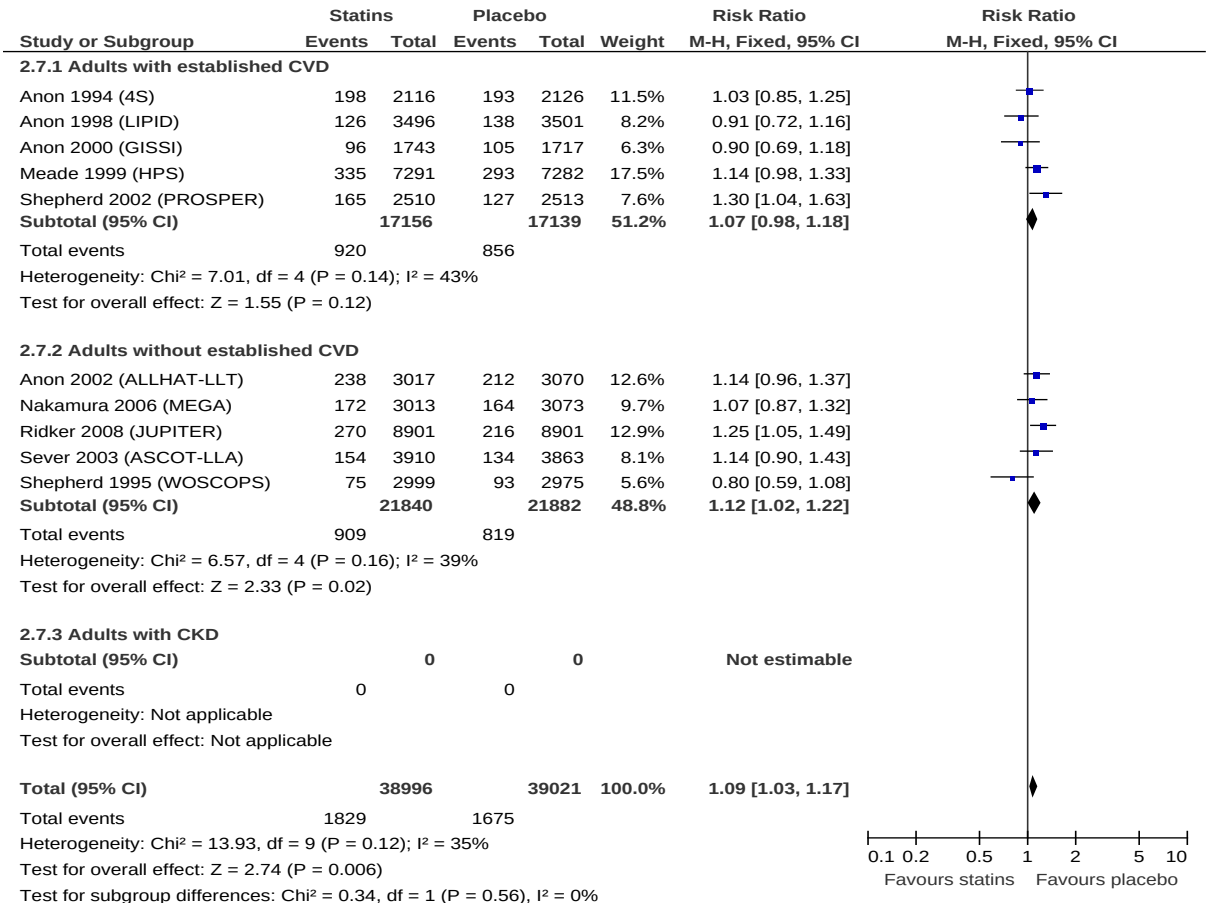
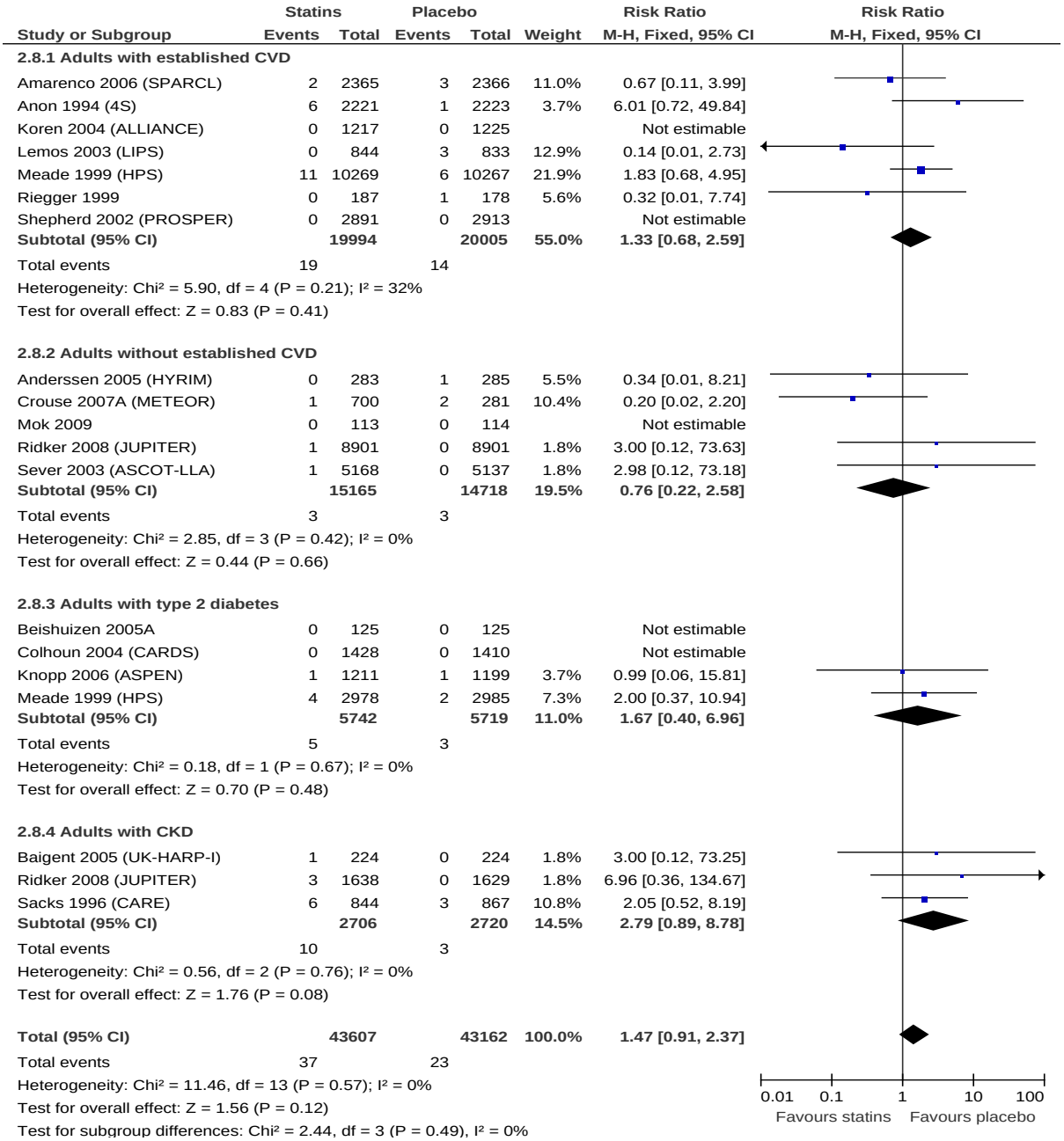


Figure 66: Adverse events: rhabdomyolysis (subgroup analysis by strata)



I.4.3 Statins versus placebo: subgroup analysis by drug and dose

Figure 67: All-cause mortality (subgroup analysis by drug and dose)

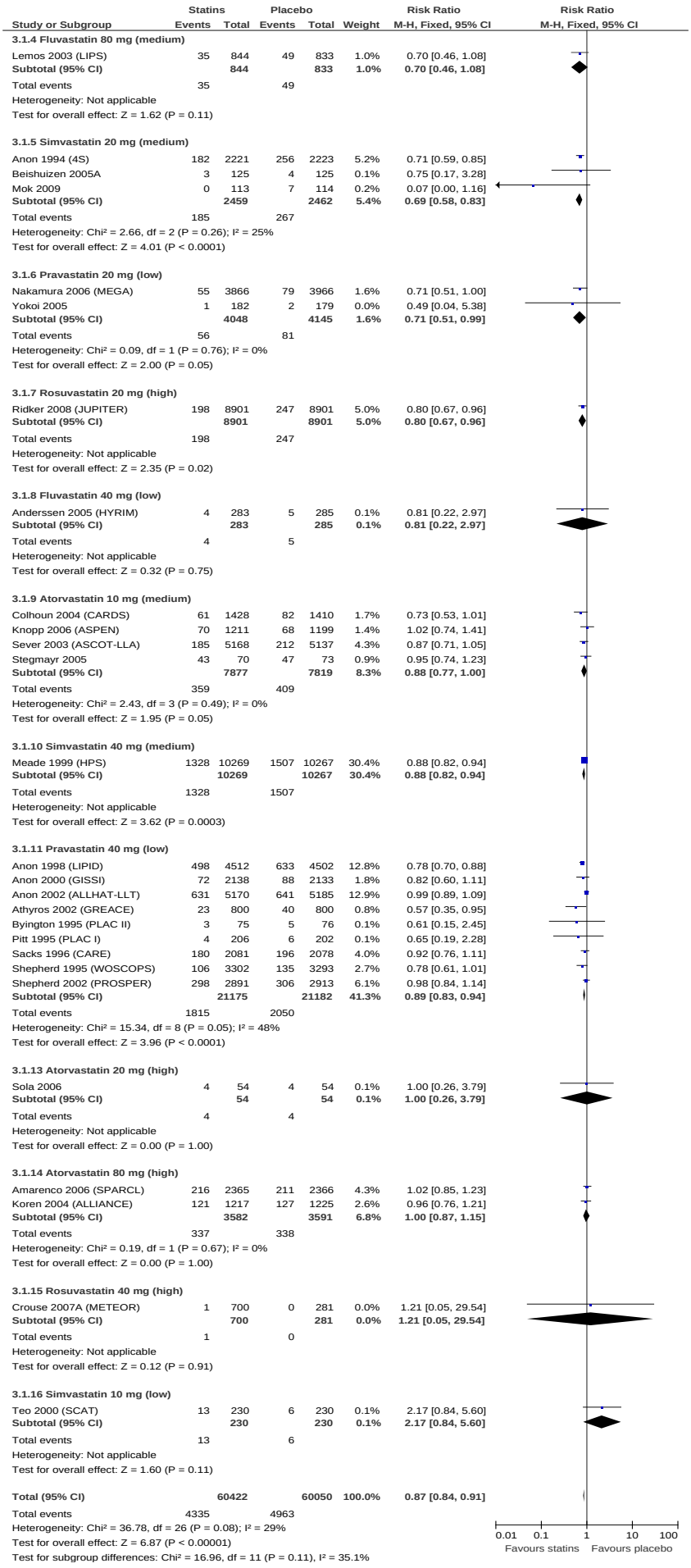

Statins
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
3.1.4 Fluvastatin 80 mg (medium)
Lemos 2003 (LIPS) 35 844 49 833 1.0% 0.70 [0.46, 1.08]
Subtotal (95% CI) 844 833 1.0% 0.70 [0.46, 1.08]
Total events 35 49
Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.11)
3.1.5 Simvastatin 20 mg (medium)
Anon 1994 (4S) 182 2221 256 2223 5.2% 0.71 [0.59, 0.85]
Beishuizen 2005A 3 125 4 125 0.1% 0.75 [0.17, 3.28]
Mok 2009 0 113 7 114 0.2% 0.07 [0.00, 1.16]
Subtotal (95% CI) 2459 2462 5.4% 0.69 [0.58, 0.83]
Total events 185 267
Heterogeneity: Chi² = 2.66, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 4.01 (P < 0.0001)
3.1.6 Pravastatin 20 mg (low)
Nakamura 2006 (MEGA) 55 3866 79 3966 1.6% 0.71 [0.51, 1.00]
Yokoi 2005 1 182 2 179 0.0% 0.49 [0.04, 5.38]
Subtotal (95% CI) 4048 4145 1.6% 0.71 [0.51, 0.99]
Total events 56 81
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)
3.1.7 Rosuvastatin 20 mg (high)
Ridker 2008 (JUPITER) 198 8901 247 8901 5.0% 0.80 [0.67, 0.96]
Subtotal (95% CI) 8901 8901 5.0% 0.80 [0.67, 0.96]
Total events 198 247
Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)
3.1.8 Fluvastatin 40 mg (low)
Anderssen 2005 (HYRIM) 4 283 5 285 0.1% 0.81 [0.22, 2.97]
Subtotal (95% CI) 283 285 0.1% 0.81 [0.22, 2.97]
Total events 4 5
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
3.1.9 Atorvastatin 10 mg (medium)
Colhoun 2004 (CARDS) 61 1428 82 1410 1.7% 0.73 [0.53, 1.01]
Knopp 2006 (ASPEN) 70 1211 68 1199 1.4% 1.02 [0.74, 1.41]
Sever 2003 (ASCOT-LLA) 185 5168 212 5137 4.3% 0.87 [0.71, 1.05]
Stegmayr 2005 43 70 47 73 0.9% 0.95 [0.74, 1.23]
Subtotal (95% CI) 7877 7819 8.3% 0.88 [0.77, 1.00]
Total events 359 409
Heterogeneity: Chi² = 2.43, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)
3.1.10 Simvastatin 40 mg (medium)
Meade 1999 (HPS) 1328 10269 1507 10267 30.4% 0.88 [0.82, 0.94]
Subtotal (95% CI) 10269 10267 30.4% 0.88 [0.82, 0.94]
Total events 1328 1507
Heterogeneity: Not applicable
Test for overall effect: Z = 3.62 (P = 0.0003)
3.1.11 Pravastatin 40 mg (low)
Anon 1998 (LIPID) 498 4512 633 4502 12.8% 0.78 [0.70, 0.88]
Anon 2000 (GISSI) 72 2138 88 2133 1.8% 0.82 [0.60, 1.11]
Anon 2002 (ALLHAT-LLT) 631 5170 641 5185 12.9% 0.99 [0.89, 1.09]
Athyros 2002 (GREACE) 23 800 40 800 0.8% 0.57 [0.35, 0.95]
Byington 1995 (PLAC II) 3 75 5 76 0.1% 0.61 [0.15, 2.45]
Pitt 1995 (PLAC I) 4 206 6 202 0.1% 0.65 [0.19, 2.28]
Sacks 1996 (CARE) 180 2081 196 2078 4.0% 0.92 [0.76, 1.11]
Shepherd 1995 (WOSCOPS) 106 3302 135 3293 2.7% 0.78 [0.61, 1.01]
Shepherd 2002 (PROSPER) 298 2891 306 2913 6.1% 0.98 [0.84, 1.14]
Subtotal (95% CI) 21175 21182 41.3% 0.89 [0.83, 0.94]
Total events 1815 2050
Heterogeneity: Chi² = 15.34, df = 8 (P = 0.05); I² = 48%
Test for overall effect: Z = 3.96 (P < 0.0001)
3.1.13 Atorvastatin 20 mg (high)
Sola 2006 4 54 4 54 0.1% 1.00 [0.26, 3.79]
Subtotal (95% CI) 54 54 0.1% 1.00 [0.26, 3.79]
Total events 4 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
3.1.14 Atorvastatin 80 mg (high)
Amarenco 2006 (SPARCL) 216 2365 211 2366 4.3% 1.02 [0.85, 1.23]
Koren 2004 (ALLIANCE) 121 1217 127 1225 2.6% 0.96 [0.76, 1.21]
Subtotal (95% CI) 3582 3591 6.8% 1.00 [0.87, 1.15]
Total events 337 338
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
3.1.15 Rosuvastatin 40 mg (high)
Crouse 2007A (METEOR) 1 700 0 281 0.0% 1.21 [0.05, 29.54]
Subtotal (95% CI) 700 281 0.0% 1.21 [0.05, 29.54]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)
3.1.16 Simvastatin 10 mg (low)
Teo 2000 (SCAT) 13 230 6 230 0.1% 2.17 [0.84, 5.60]
Subtotal (95% CI) 230 230 0.1% 2.17 [0.84, 5.60]
Total events 13 6
Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)
Total (95% CI) 60422 60050 100.0% 0.87 [0.84, 0.91]
Total events 4335 4963
Heterogeneity: Chi² = 36.78, df = 26 (P = 0.08); I² = 29%
Test for overall effect: Z = 6.87 (P < 0.00001)
Test for subgroup differences: Chi² = 16.96, df = 11 (P = 0.11), I² = 35.1%
0.01 0.1 1 10 100
Favours statins Favours placebo

Figure 68: CV mortality (subgroup analysis by drug and dose)

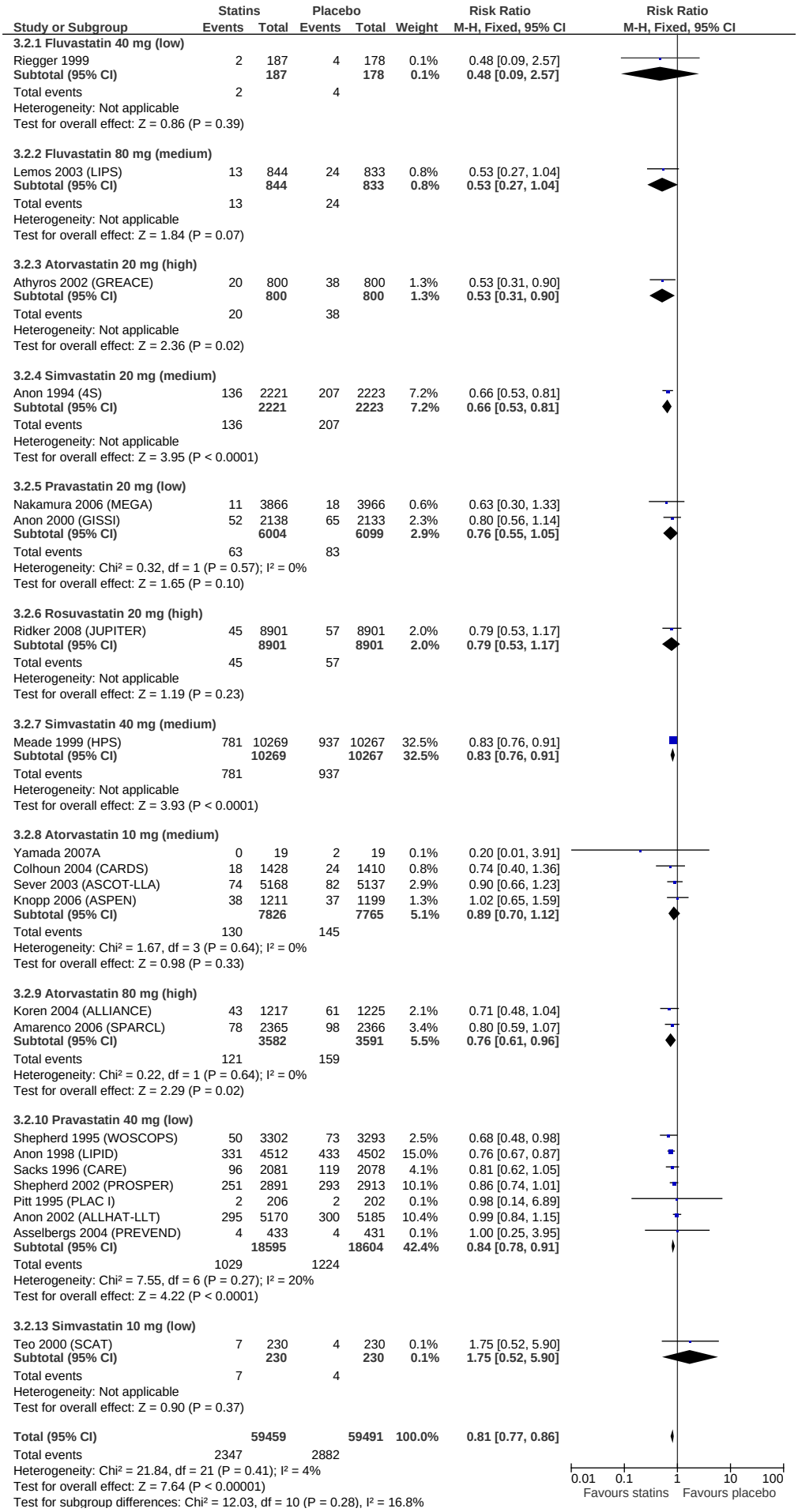
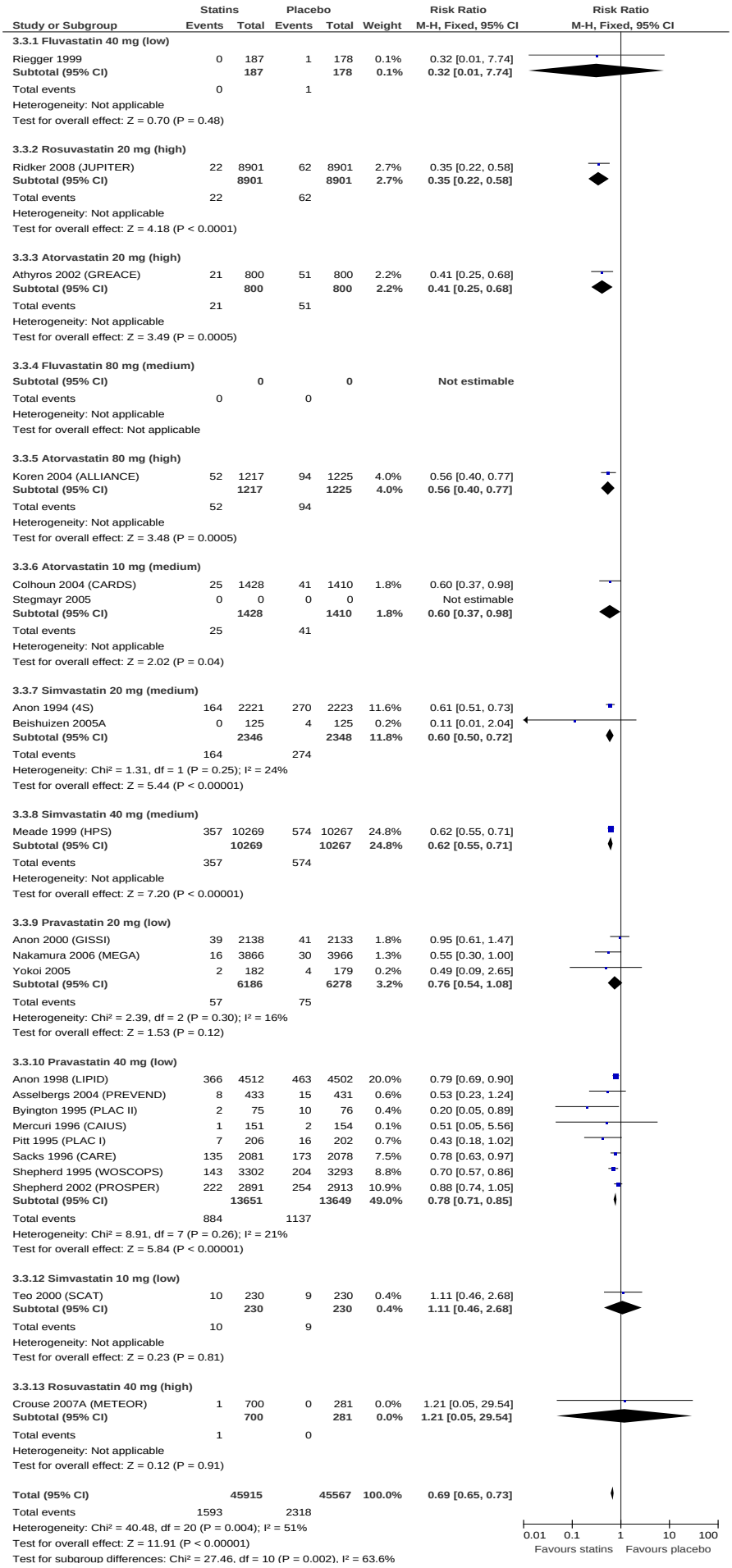

Statins
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
3.2.1 Fluvastatin 40 mg (low)
Riegger 1999 2 187 4 178 0.1% 0.48 [0.09, 2.57]
Subtotal (95% CI) 187 178 0.1% 0.48 [0.09, 2.57]
Total events 2 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
3.2.2 Fluvastatin 80 mg (medium)
Lemos 2003 (LIPS) 13 844 24 833 0.8% 0.53 [0.27, 1.04]
Subtotal (95% CI) 844 833 0.8% 0.53 [0.27, 1.04]
Total events 13 24
Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)
3.2.3 Atorvastatin 20 mg (high)
Athyros 2002 (GREACE) 20 800 38 800 1.3% 0.53 [0.31, 0.90]
Subtotal (95% CI) 800 800 1.3% 0.53 [0.31, 0.90]
Total events 20 38
Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)
3.2.4 Simvastatin 20 mg (medium)
Anon 1994 (4S) 136 2221 207 2223 7.2% 0.66 [0.53, 0.81]
Subtotal (95% CI) 2221 2223 7.2% 0.66 [0.53, 0.81]
Total events 136 207
Heterogeneity: Not applicable
Test for overall effect: Z = 3.95 (P < 0.0001)
3.2.5 Pravastatin 20 mg (low)
Nakamura 2006 (MEGA) 11 3866 18 3966 0.6% 0.63 [0.30, 1.33]
Anon 2000 (GISSI) 52 2138 65 2133 2.3% 0.80 [0.56, 1.14]
Subtotal (95% CI) 6004 6099 2.9% 0.76 [0.55, 1.05]
Total events 63 83
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)
3.2.6 Rosuvastatin 20 mg (high)
Ridker 2008 (JUPITER) 45 8901 57 8901 2.0% 0.79 [0.53, 1.17]
Subtotal (95% CI) 8901 8901 2.0% 0.79 [0.53, 1.17]
Total events 45 57
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
3.2.7 Simvastatin 40 mg (medium)
Meade 1999 (HPS) 781 10269 937 10267 32.5% 0.83 [0.76, 0.91]
Subtotal (95% CI) 10269 10267 32.5% 0.83 [0.76, 0.91]
Total events 781 937
Heterogeneity: Not applicable
Test for overall effect: Z = 3.93 (P < 0.0001)
3.2.8 Atorvastatin 10 mg (medium)
Yamada 2007A 0 19 2 19 0.1% 0.20 [0.01, 3.91]
Colhoun 2004 (CARDS) 18 1428 24 1410 0.8% 0.74 [0.40, 1.36]
Sever 2003 (ASCOT-LLA) 74 5168 82 5137 2.9% 0.90 [0.66, 1.23]
Knopp 2006 (ASPEN) 38 1211 37 1199 1.3% 1.02 [0.65, 1.59]
Subtotal (95% CI) 7826 7765 5.1% 0.89 [0.70, 1.12]
Total events 130 145
Heterogeneity: Chi² = 1.67, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)
3.2.9 Atorvastatin 80 mg (high)
Koren 2004 (ALLIANCE) 43 1217 61 1225 2.1% 0.71 [0.48, 1.04]
Amarenco 2006 (SPARCL) 78 2365 98 2366 3.4% 0.80 [0.59, 1.07]
Subtotal (95% CI) 3582 3591 5.5% 0.76 [0.61, 0.96]
Total events 121 159
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)
3.2.10 Pravastatin 40 mg (low)
Shepherd 1995 (WOSCOPS) 50 3302 73 3293 2.5% 0.68 [0.48, 0.98]
Anon 1998 (LIPID) 331 4512 433 4502 15.0% 0.76 [0.67, 0.87]
Sacks 1996 (CARE) 96 2081 119 2078 4.1% 0.81 [0.62, 1.05]
Shepherd 2002 (PROSPER) 251 2891 293 2913 10.1% 0.86 [0.74, 1.01]
Pitt 1995 (PLAC I) 2 206 2 202 0.1% 0.98 [0.14, 6.89]
Anon 2002 (ALLHAT-LLT) 295 5170 300 5185 10.4% 0.99 [0.84, 1.15]
Asselbergs 2004 (PREVEND) 4 433 4 431 0.1% 1.00 [0.25, 3.95]
Subtotal (95% CI) 18595 18604 42.4% 0.84 [0.78, 0.91]
Total events 1029 1224
Heterogeneity: Chi² = 7.55, df = 6 (P = 0.27); I² = 20%
Test for overall effect: Z = 4.22 (P < 0.0001)
3.2.13 Simvastatin 10 mg (low)
Teo 2000 (SCAT) 7 230 4 230 0.1% 1.75 [0.52, 5.90]
Subtotal (95% CI) 230 230 0.1% 1.75 [0.52, 5.90]
Total events 7 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)
Total (95% CI) 59459 59491 100.0% 0.81 [0.77, 0.86]
Total events 2347 2882
Heterogeneity: Chi² = 21.84, df = 21 (P = 0.41); I² = 4%
Test for overall effect: Z = 7.64 (P < 0.00001)
Test for subgroup differences: Chi² = 12.03, df = 10 (P = 0.28), I² = 16.8%
0.01 0.1 1 10 100
Favours statins Favours placebo

Figure 69: Non-fatal MI (subgroup analysis by drug and dose)


Statins
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
3.3.1 Fluvastatin 40 mg (low)
Riegger 1999 0 187 1 178 0.1% 0.32 [0.01, 7.74]
Subtotal (95% CI) 187 178 0.1% 0.32 [0.01, 7.74]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
3.3.2 Rosuvastatin 20 mg (high)
Ridker 2008 (JUPITER) 22 8901 62 8901 2.7% 0.35 [0.22, 0.58]
Subtotal (95% CI) 8901 8901 2.7% 0.35 [0.22, 0.58]
Total events 22 62
Heterogeneity: Not applicable
Test for overall effect: Z = 4.18 (P < 0.0001)
3.3.3 Atorvastatin 20 mg (high)
Athyros 2002 (GREACE) 21 800 51 800 2.2% 0.41 [0.25, 0.68]
Subtotal (95% CI) 800 800 2.2% 0.41 [0.25, 0.68]
Total events 21 51
Heterogeneity: Not applicable
Test for overall effect: Z = 3.49 (P = 0.0005)
3.3.4 Fluvastatin 80 mg (medium)
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
3.3.5 Atorvastatin 80 mg (high)
Koren 2004 (ALLIANCE) 52 1217 94 1225 4.0% 0.56 [0.40, 0.77]
Subtotal (95% CI) 1217 1225 4.0% 0.56 [0.40, 0.77]
Total events 52 94
Heterogeneity: Not applicable
Test for overall effect: Z = 3.48 (P = 0.0005)
3.3.6 Atorvastatin 10 mg (medium)
Colhoun 2004 (CARDS) 25 1428 41 1410 1.8% 0.60 [0.37, 0.98]
Stegmayr 2005 0 0 0 0 Not estimable
Subtotal (95% CI) 1428 1410 1.8% 0.60 [0.37, 0.98]
Total events 25 41
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)
3.3.7 Simvastatin 20 mg (medium)
Anon 1994 (4S) 164 2221 270 2223 11.6% 0.61 [0.51, 0.73]
Beishuizen 2005A 0 125 4 125 0.2% 0.11 [0.01, 2.04]
Subtotal (95% CI) 2346 2348 11.8% 0.60 [0.50, 0.72]
Total events 164 274
Heterogeneity: Chi² = 1.31, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 5.44 (P < 0.00001)
3.3.8 Simvastatin 40 mg (medium)
Meade 1999 (HPS) 357 10269 574 10267 24.8% 0.62 [0.55, 0.71]
Subtotal (95% CI) 10269 10267 24.8% 0.62 [0.55, 0.71]
Total events 357 574
Heterogeneity: Not applicable
Test for overall effect: Z = 7.20 (P < 0.00001)
3.3.9 Pravastatin 20 mg (low)
Anon 2000 (GISSI) 39 2138 41 2133 1.8% 0.95 [0.61, 1.47]
Nakamura 2006 (MEGA) 16 3866 30 3966 1.3% 0.55 [0.30, 1.00]
Yokoi 2005 2 182 4 179 0.2% 0.49 [0.09, 2.65]
Subtotal (95% CI) 6186 6278 3.2% 0.76 [0.54, 1.08]
Total events 57 75
Heterogeneity: Chi² = 2.39, df = 2 (P = 0.30); I² = 16%
Test for overall effect: Z = 1.53 (P = 0.12)
3.3.10 Pravastatin 40 mg (low)
Anon 1998 (LIPID) 366 4512 463 4502 20.0% 0.79 [0.69, 0.90]
Asselbergs 2004 (PREVEND) 8 433 15 431 0.6% 0.53 [0.23, 1.24]
Byington 1995 (PLAC II) 2 75 10 76 0.4% 0.20 [0.05, 0.89]
Mercuri 1996 (CAIUS) 1 151 2 154 0.1% 0.51 [0.05, 5.56]
Pitt 1995 (PLAC I) 7 206 16 202 0.7% 0.43 [0.18, 1.02]
Sacks 1996 (CARE) 135 2081 173 2078 7.5% 0.78 [0.63, 0.97]
Shepherd 1995 (WOSCOPS) 143 3302 204 3293 8.8% 0.70 [0.57, 0.86]
Shepherd 2002 (PROSPER) 222 2891 254 2913 10.9% 0.88 [0.74, 1.05]
Subtotal (95% CI) 13651 13649 49.0% 0.78 [0.71, 0.85]
Total events 884 1137
Heterogeneity: Chi² = 8.91, df = 7 (P = 0.26); I² = 21%
Test for overall effect: Z = 5.84 (P < 0.00001)
3.3.12 Simvastatin 10 mg (low)
Teo 2000 (SCAT) 10 230 9 230 0.4% 1.11 [0.46, 2.68]
Subtotal (95% CI) 230 230 0.4% 1.11 [0.46, 2.68]
Total events 10 9
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)
3.3.13 Rosuvastatin 40 mg (high)
Crouse 2007A (METEOR) 1 700 0 281 0.0% 1.21 [0.05, 29.54]
Subtotal (95% CI) 700 281 0.0% 1.21 [0.05, 29.54]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)
Total (95% CI) 45915 45567 100.0% 0.69 [0.65, 0.73]
Total events 1593 2318
Heterogeneity: Chi² = 40.48, df = 20 (P = 0.004); I² = 51%
Test for overall effect: Z = 11.91 (P < 0.00001)
Test for subgroup differences: Chi² = 27.46, df = 10 (P = 0.002), I² = 63.6%
0.01 0.1 1 10 100
Favours statins Favours placebo

I.4.4 Statins versus placebo: subgroup analysis by follow-up time

Figure 70: All-cause mortality (subgroup analysis by follow up time)

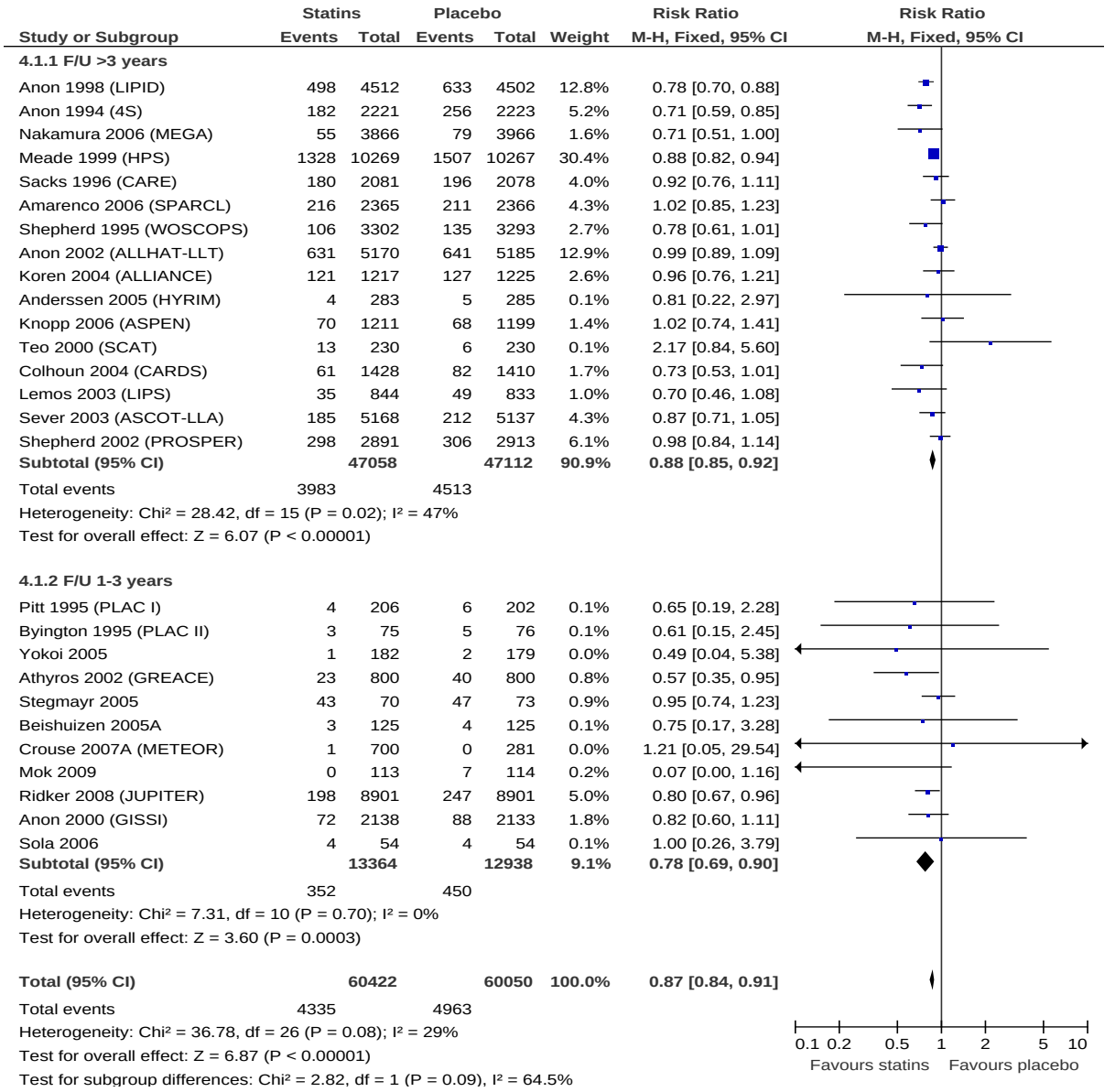


Figure 71: CV mortality (subgroup analysis by follow up time)

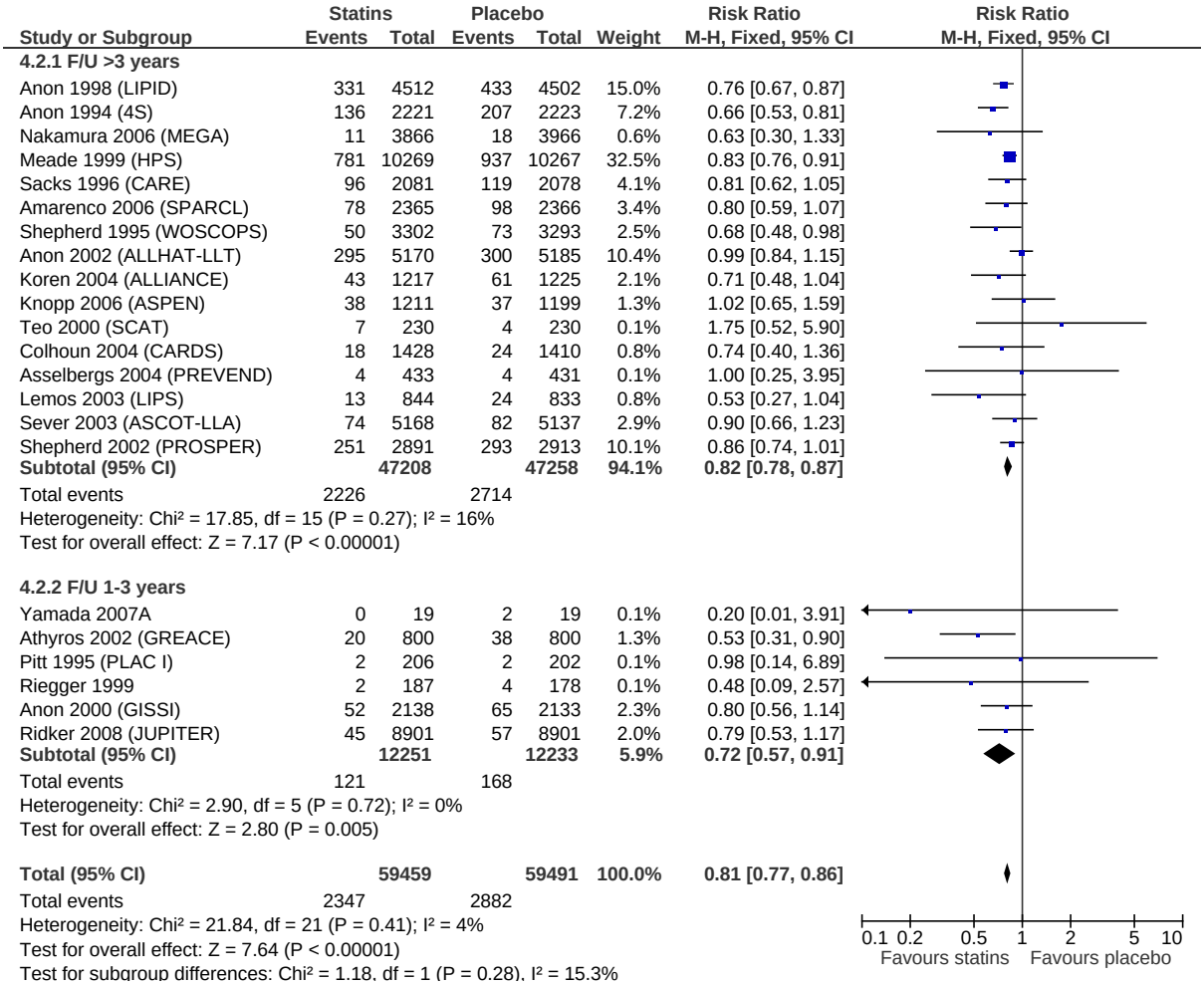


Figure 72: Non-fatal MI (subgroup analysis by follow up time)

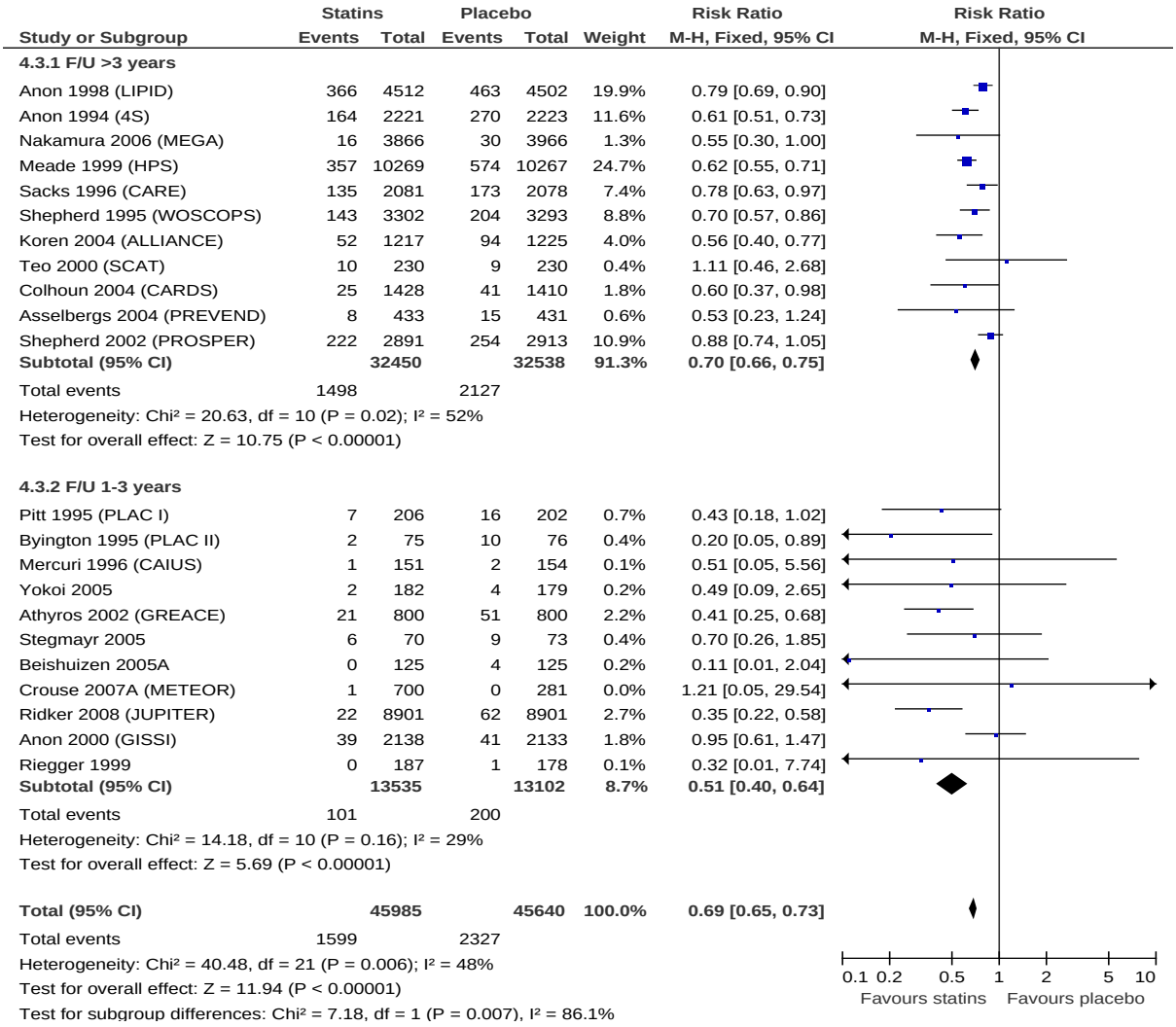
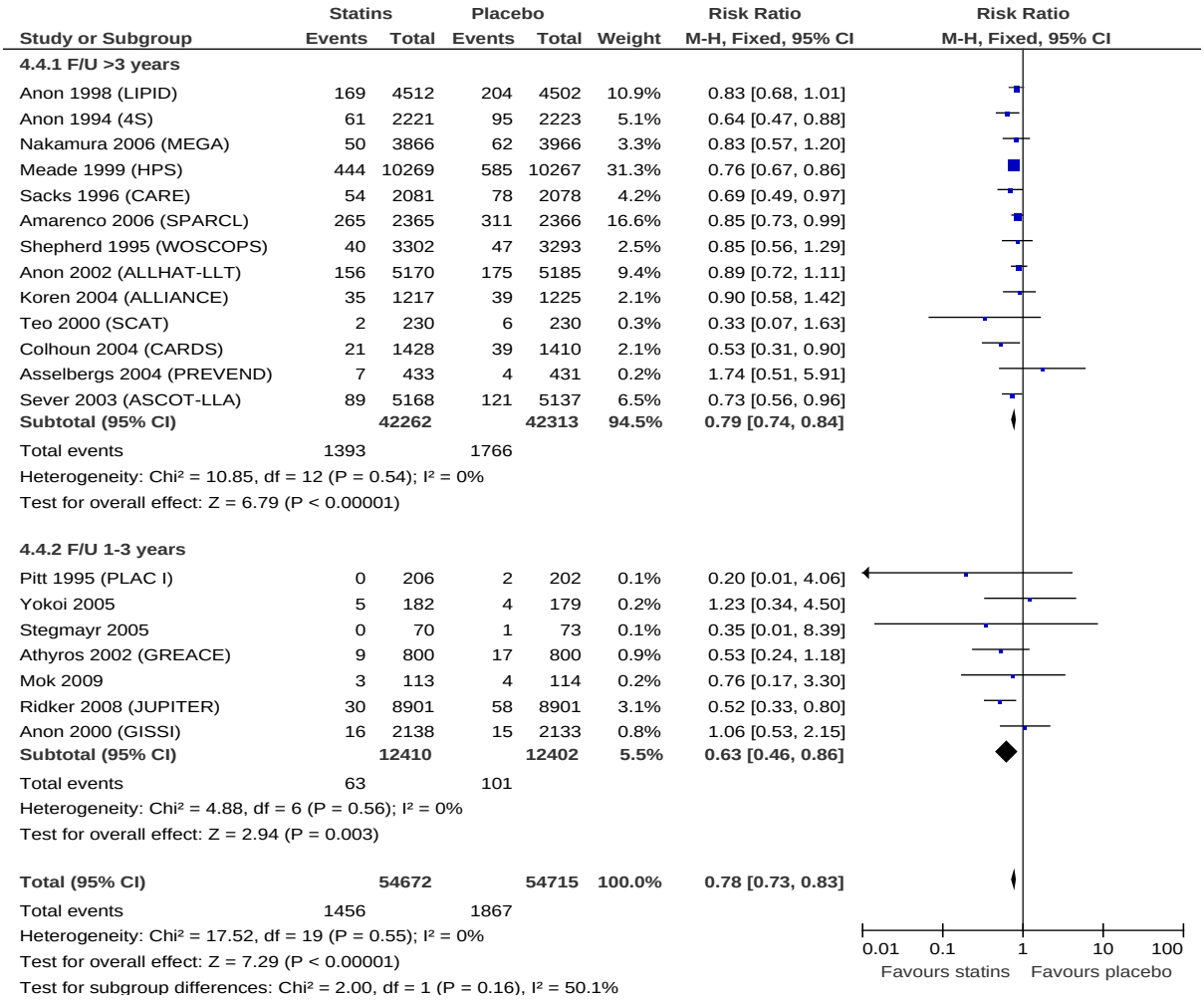


Figure 73: Stroke (subgroup analysis by follow up time)



I.4.5 Statins versus placebo: time-to-event analysis. Subgroup analysis by statin intensity

Figure 74: All-cause mortality (subgroup analysis by statin intensity, time to event analysis)

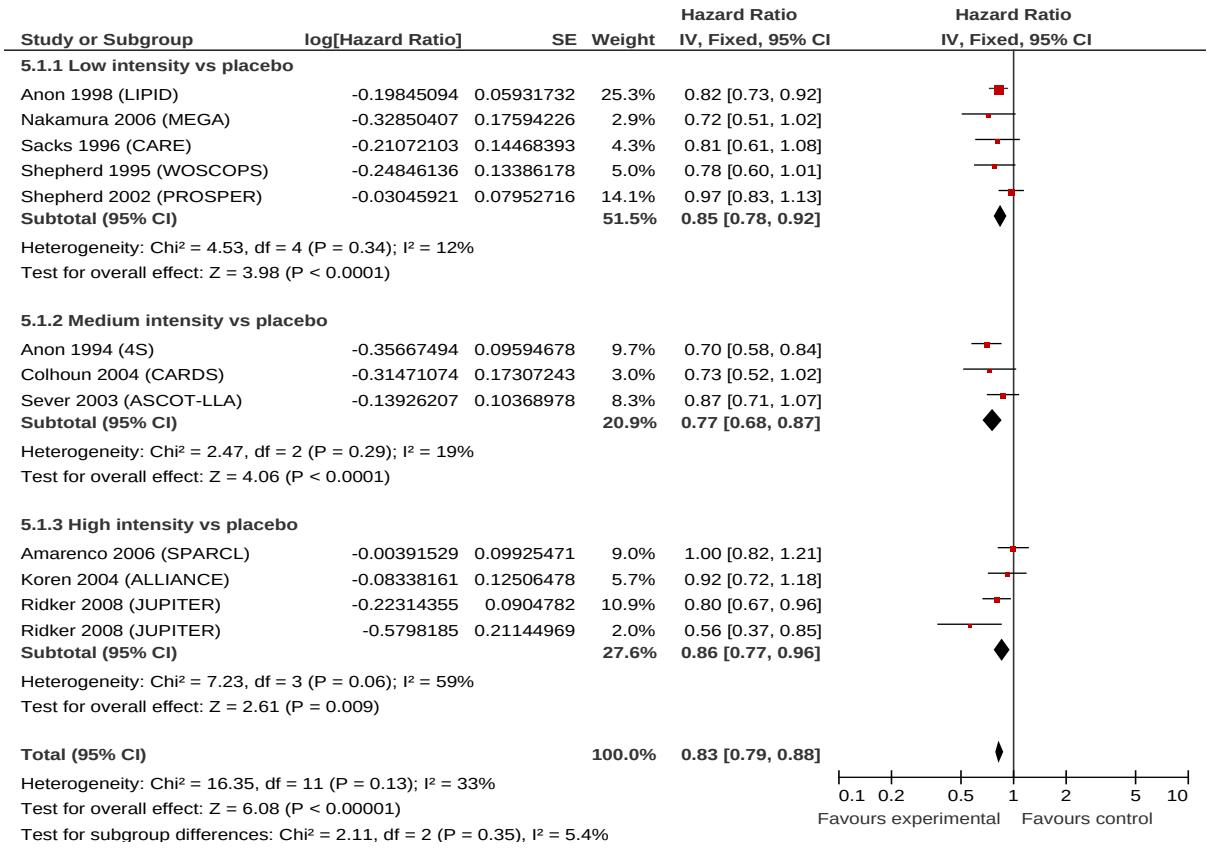


Figure 75: CV mortality (subgroup analysis by statin intensity, time to event analysis)

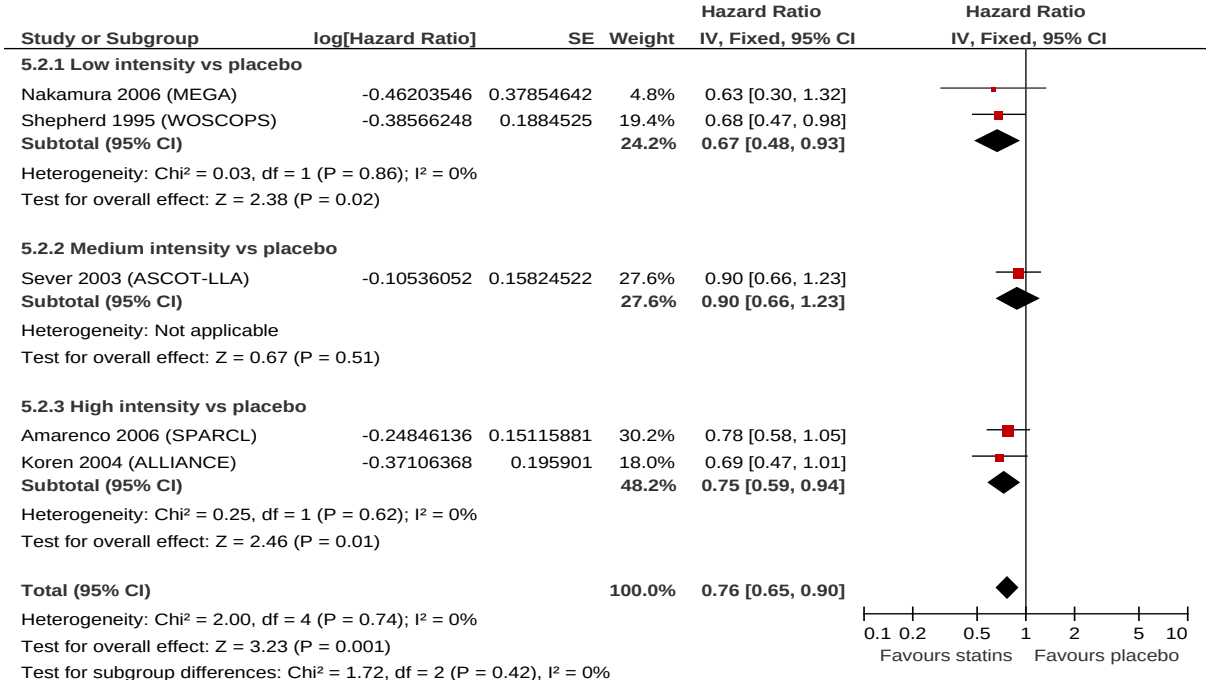


Figure 76: Non-fatal MI (subgroup analysis by statin intensity, time to event analysis)

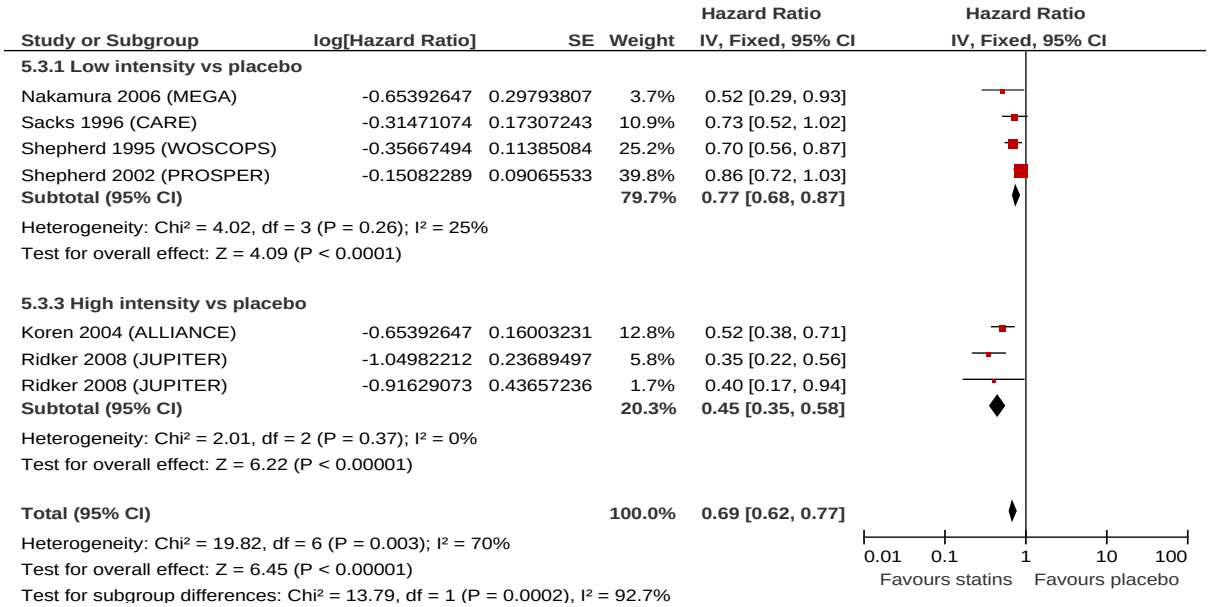
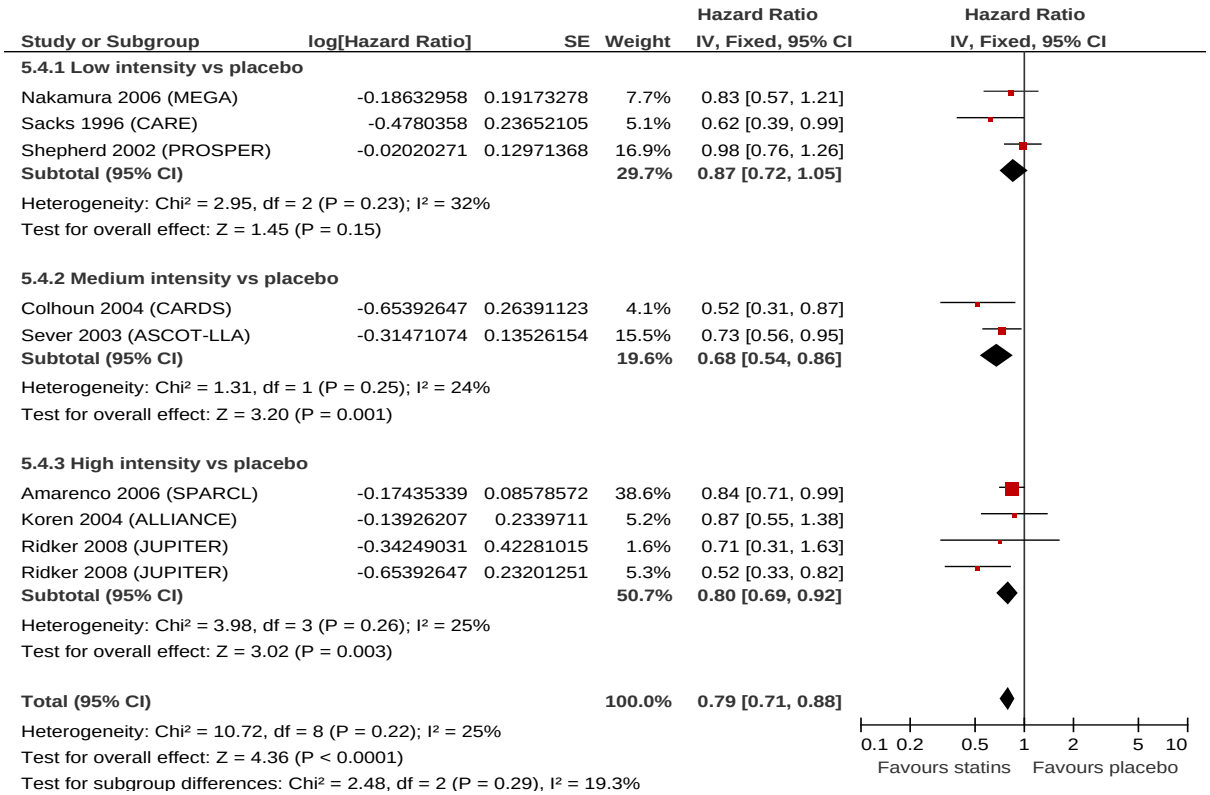


Figure 77: Stroke (subgroup analysis by statin intensity, time to event analysis)



I.4.6 Statins versus placebo: time-to-event analysis. Subgroup analysis by strata

Figure 78: All-cause mortality (subgroup analysis by strata, time to event analysis)

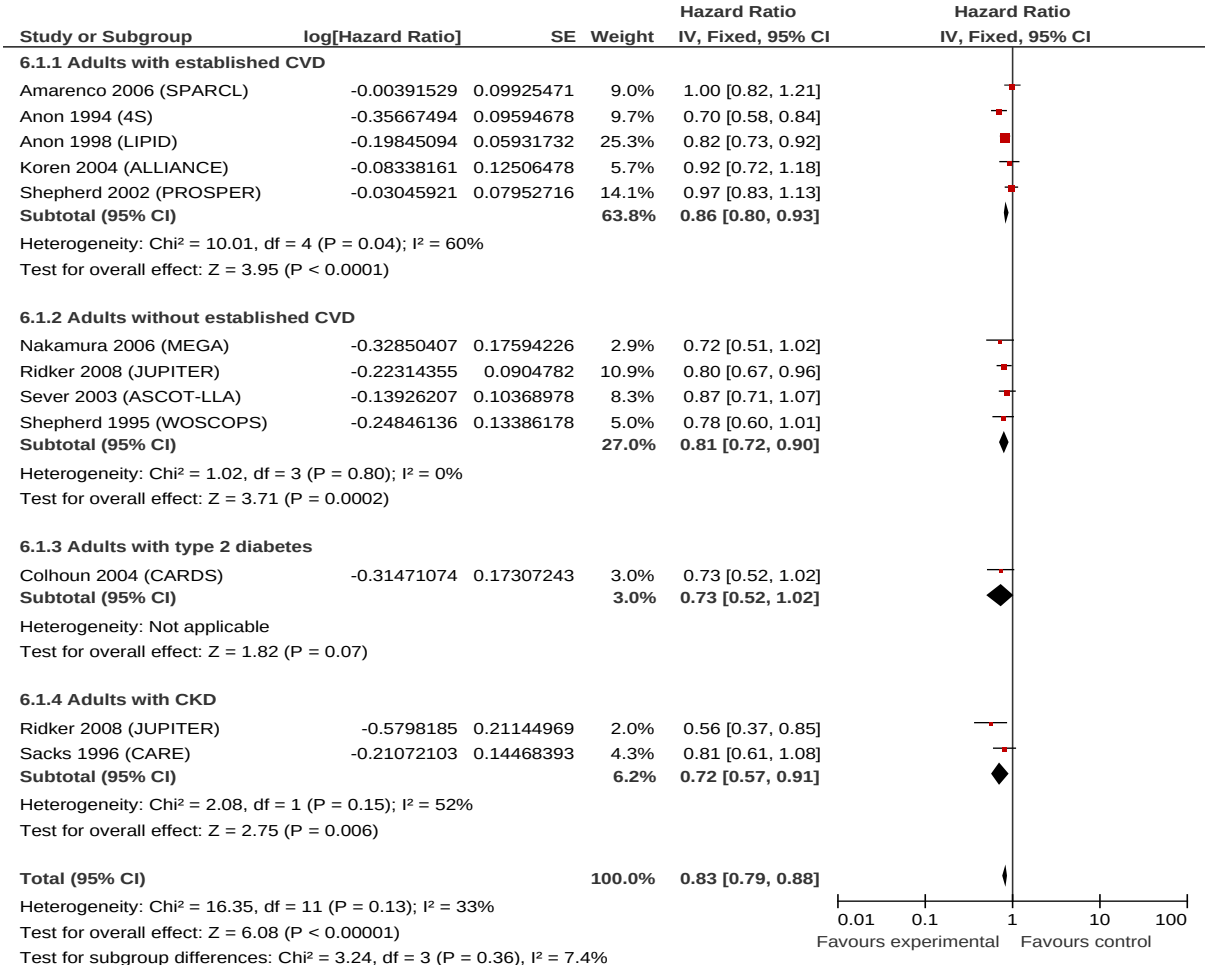


Figure 79: CV mortality (subgroup analysis by strata, time to event analysis)

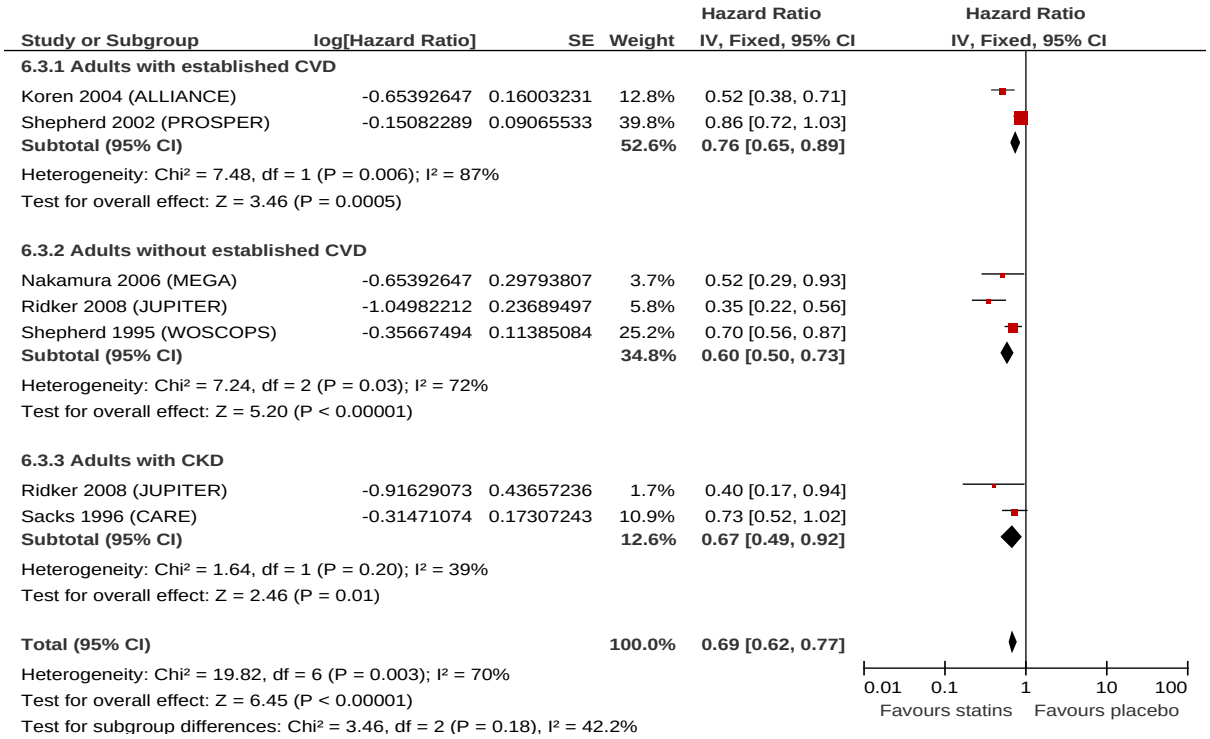


Figure 80: Non-fatal MI (subgroup analysis by strata, time to event analysis)

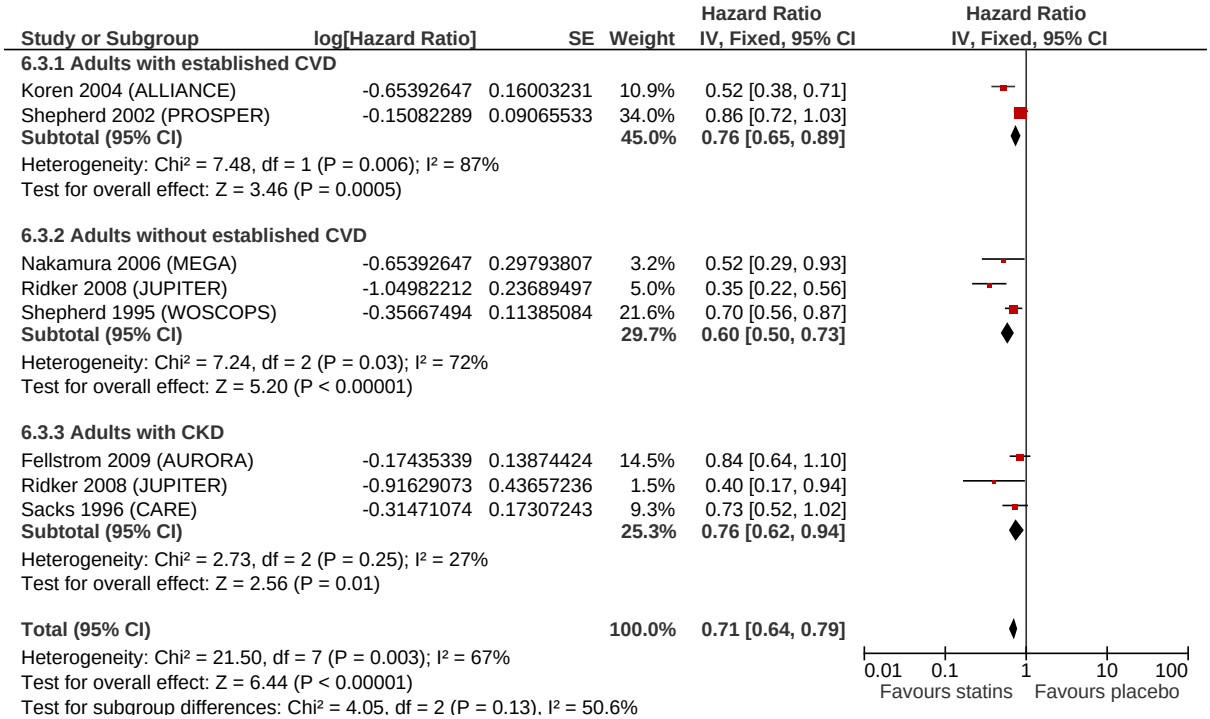
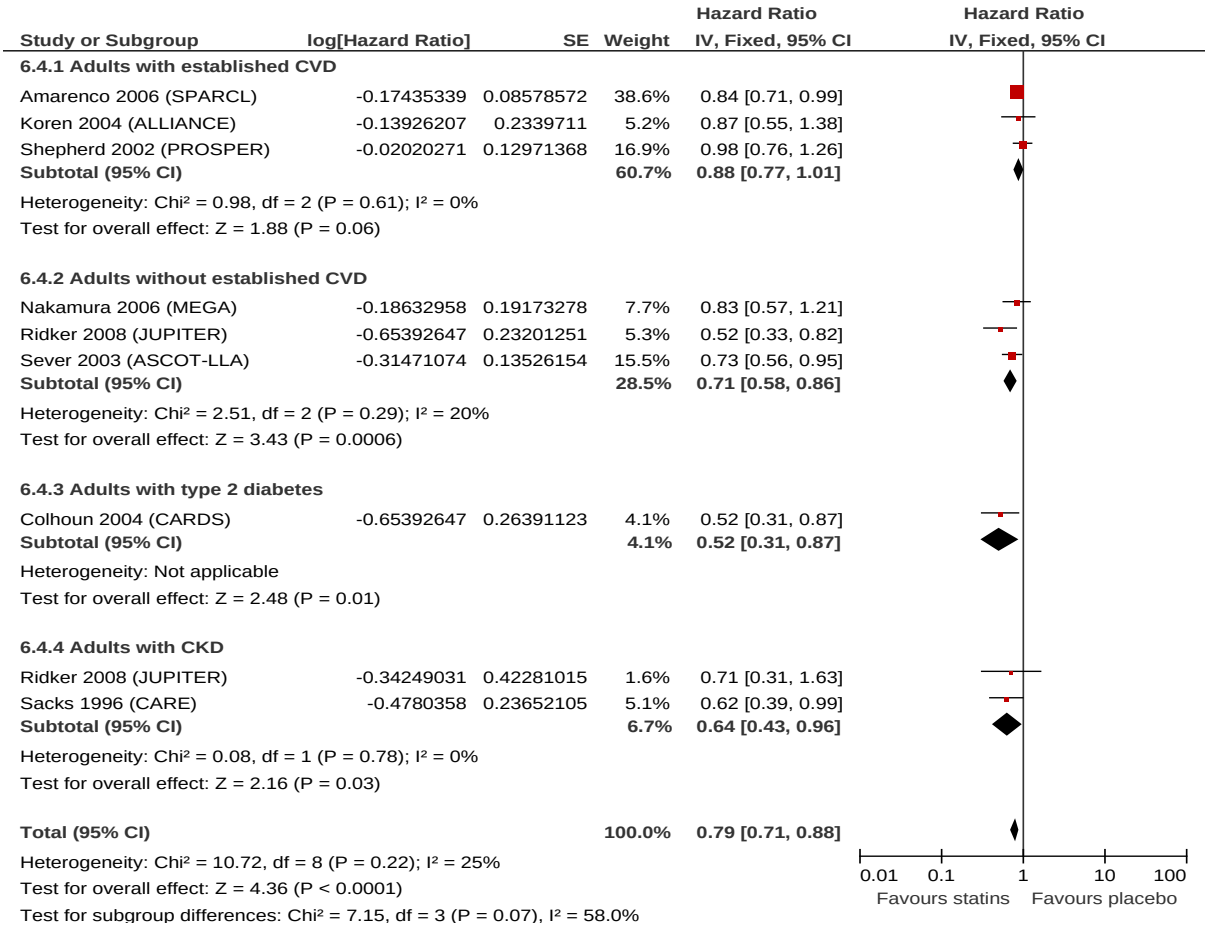
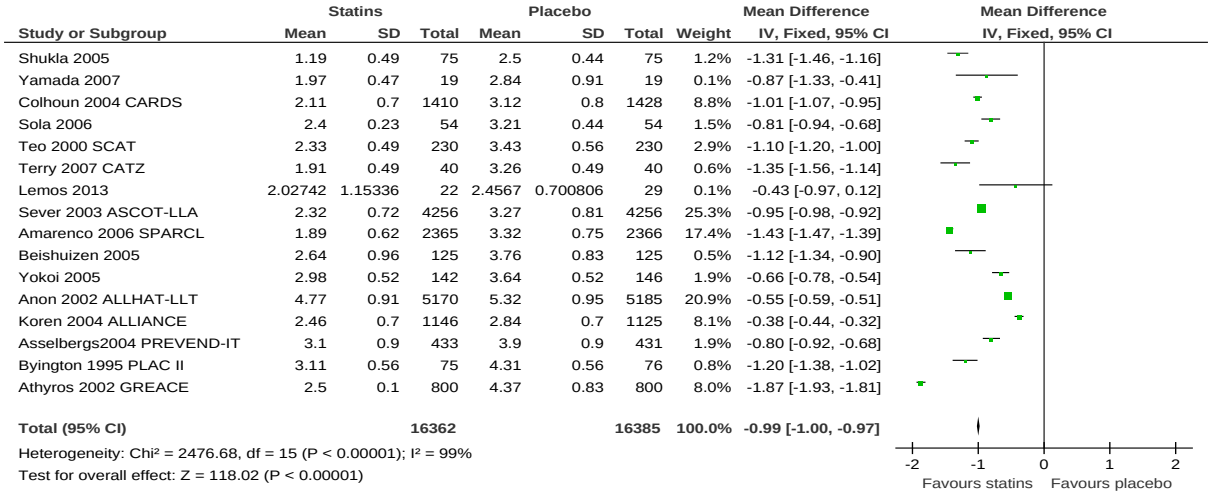


Figure 81: Stroke (subgroup analysis by strata, time to event analysis)



I.4.7 Statin versus placebo: LDL-cholesterol reduction

Figure 82: LDL-cholesterol (mmol/l): studies ranked according to baseline LDL-cholesterol

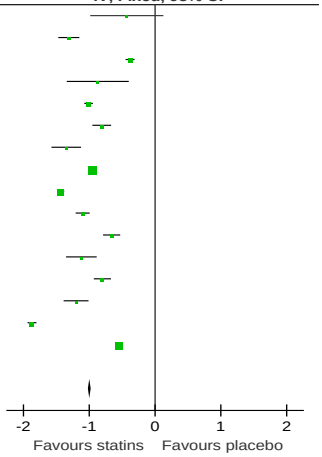


Studies in ascending order according to baseline LDL-cholesterol value

Figure 83: LDL-cholesterol (mmol/l): studies ranked according to placebo LDL-cholesterol at follow-up

Study or Subgroup	Statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lemos 2013	2.02742	1.15336	22	2.4567	0.700806	29	0.1%	-0.43 [-0.97, 0.12]
Shukla 2005	1.19	0.49	75	2.5	0.44	75	1.2%	-1.31 [-1.46, -1.16]
Koren 2004 ALLIANCE	2.46	0.7	1146	2.84	0.7	1125	8.1%	-0.38 [-0.44, -0.32]
Yamada 2007	1.97	0.47	19	2.84	0.91	19	0.1%	-0.87 [-1.33, -0.41]
Colhoun 2004 CARDS	2.11	0.7	1410	3.12	0.8	1428	8.8%	-1.01 [-1.07, -0.95]
Sola 2006	2.4	0.23	54	3.21	0.44	54	1.5%	-0.81 [-0.94, -0.68]
Terry 2007 CATZ	1.91	0.49	40	3.26	0.49	40	0.6%	-1.35 [-1.56, -1.14]
Sever 2003 ASCOT-LLA	2.32	0.72	4256	3.27	0.81	4256	25.3%	-0.95 [-0.98, -0.92]
Amarenco 2006 SPARCL	1.89	0.62	2365	3.32	0.75	2366	17.4%	-1.43 [-1.47, -1.39]
Teo 2000 SCAT	2.33	0.49	230	3.43	0.56	230	2.9%	-1.10 [-1.20, -1.00]
Yokoi 2005	2.98	0.52	142	3.64	0.52	146	1.9%	-0.66 [-0.78, -0.54]
Beishuizen 2005	2.64	0.96	125	3.76	0.83	125	0.5%	-1.12 [-1.34, -0.90]
Asselbergs2004 PREVEND-IT	3.1	0.9	433	3.9	0.9	431	1.9%	-0.80 [-0.92, -0.68]
Byington 1995 PLAC II	3.11	0.56	75	4.31	0.56	76	0.8%	-1.20 [-1.38, -1.02]
Athyros 2002 GREACE	2.5	0.1	800	4.37	0.83	800	8.0%	-1.87 [-1.93, -1.81]
Anon 2002 ALLHAT-LLT	4.77	0.91	5170	5.32	0.95	5185	20.9%	-0.55 [-0.59, -0.51]
Total (95% CI)			**16362**			**16385**	**100.0%**	**-0.99 [-1.00, -0.97]**

Heterogeneity: Chi² = 2476.68, df = 15 (P < 0.00001); I² = 99%
Test for overall effect: Z = 118.02 (P < 0.00001)



Studies in ascending order according to final placebo LDL-cholesterol value

Figure 84: LDL-cholesterol (mmol/l): subgroup analysis according to statin intensity

Study or Subgroup	Statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Low intensity								
Anon 2002 ALLHAT-LLT	4.77	0.91	5170	5.32	0.95	5185	20.9%	-0.55 [-0.59, -0.51]
Asselbergs2004 PREVEND-IT	3.1	0.9	433	3.9	0.9	431	1.9%	-0.80 [-0.92, -0.68]
Byington 1995 PLAC II	3.11	0.56	75	4.31	0.56	76	0.8%	-1.20 [-1.38, -1.02]
Teo 2000 SCAT	2.33	0.49	230	3.43	0.56	230	2.9%	-1.10 [-1.20, -1.00]
Yokoi 2005	2.98	0.52	142	3.64	0.52	146	1.9%	-0.66 [-0.78, -0.54]
Subtotal (95% CI)			**6050**			**6068**	**28.3%**	**-0.65 [-0.68, -0.62]**
Heterogeneity: Chi² = 156.47, df = 4 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 41.37 (P < 0.00001)								
1.3.2 Medium intensity								
Beishuizen 2005	2.64	0.96	125	3.76	0.83	125	0.5%	-1.12 [-1.34, -0.90]
Colhoun 2004 CARDS	2.11	0.7	1410	3.12	0.8	1428	8.8%	-1.01 [-1.07, -0.95]
Sever 2003 ASCOT-LLA	2.32	0.72	4256	3.27	0.81	4256	25.3%	-0.95 [-0.98, -0.92]
Shukla 2005	1.19	0.49	75	2.5	0.44	75	1.2%	-1.31 [-1.46, -1.16]
Yamada 2007	1.97	0.47	19	2.84	0.91	19	0.1%	-0.87 [-1.33, -0.41]
Subtotal (95% CI)			**5885**			**5903**	**35.9%**	**-0.98 [-1.01, -0.95]**
Heterogeneity: Chi² = 24.96, df = 4 (P < 0.0001); I² = 84%								
Test for overall effect: Z = 70.25 (P < 0.00001)								
1.3.3 High intensity								
Amarenco 2006 SPARCL	1.89	0.62	2365	3.32	0.75	2366	17.4%	-1.43 [-1.47, -1.39]
Athyros 2002 GREACE	2.5	0.1	800	4.37	0.83	800	8.0%	-1.87 [-1.93, -1.81]
Koren 2004 ALLIANCE	2.46	0.7	1146	2.84	0.7	1125	8.1%	-0.38 [-0.44, -0.32]
Lemos 2013	2.02742	1.15336	22	2.4567	0.700806	29	0.1%	-0.43 [-0.97, 0.12]
Sola 2006	2.4	0.23	54	3.21	0.44	54	1.5%	-0.81 [-0.94, -0.68]
Terry 2007 CATZ	1.91	0.49	40	3.26	0.49	40	0.6%	-1.35 [-1.56, -1.14]
Subtotal (95% CI)			**4427**			**4414**	**35.7%**	**-1.26 [-1.29, -1.23]**
Heterogeneity: Chi² = 1449.28, df = 5 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 90.15 (P < 0.00001)								
Total (95% CI)			**16362**			**16385**	**100.0%**	**-0.99 [-1.00, -0.97]**
Heterogeneity: Chi² = 2476.68, df = 15 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 118.02 (P < 0.00001)								
Test for subgroup differences: Chi² = 845.97, df = 2 (P < 0.00001), I² = 99.8%								

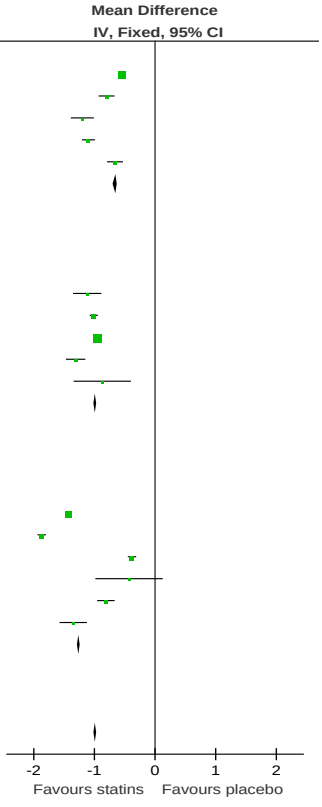
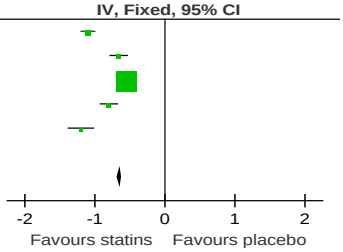


Figure 85: LDL-cholesterol (mmol/l): low intensity statin studies ranked according to baseline LDL-cholesterol

Study or Subgroup	Statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Teo 2000 SCAT	2.33	0.49	230	3.43	0.56	230	10.2%	-1.10 [-1.20, -1.00]
Yokoi 2005	2.98	0.52	142	3.64	0.52	146	6.6%	-0.66 [-0.78, -0.54]
Anon 2002 ALLHAT-LLT	4.77	0.91	5170	5.32	0.95	5185	73.7%	-0.55 [-0.59, -0.51]
Asselbergs2004 PREVEND-IT	3.1	0.9	433	3.9	0.9	431	6.6%	-0.80 [-0.92, -0.68]
Byington 1995 PLAC II	3.11	0.56	75	4.31	0.56	76	3.0%	-1.20 [-1.38, -1.02]
Total (95% CI)			**6050**			**6068**	**100.0%**	**-0.65 [-0.68, -0.62]**

Heterogeneity: Chi² = 156.47, df = 4 (P < 0.00001); I² = 97%
Test for overall effect: Z = 41.37 (P < 0.00001)

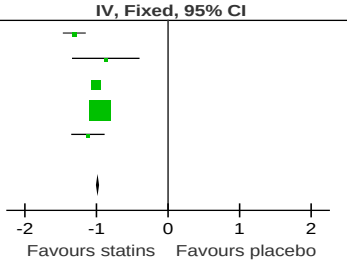


Studies in ascending order according to baseline LDL-cholesterol value

Figure 86: LDL-cholesterol (mmol/l): medium intensity statin studies ranked according to baseline LDL-cholesterol

Study or Subgroup	Statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Shukla 2005	1.19	0.49	75	2.5	0.44	75	3.4%	-1.31 [-1.46, -1.16]
Yamada 2007	1.97	0.47	19	2.84	0.91	19	0.4%	-0.87 [-1.33, -0.41]
Colhoun 2004 CARDS	2.11	0.7	1410	3.12	0.8	1428	24.4%	-1.01 [-1.07, -0.95]
Sever 2003 ASCOT-LLA	2.32	0.72	4256	3.27	0.81	4256	70.4%	-0.95 [-0.98, -0.92]
Beishuizen 2005	2.64	0.96	125	3.76	0.83	125	1.5%	-1.12 [-1.34, -0.90]
Total (95% CI)			**5885**			**5903**	**100.0%**	**-0.98 [-1.01, -0.95]**

Heterogeneity: Chi² = 24.96, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 70.25 (P < 0.00001)

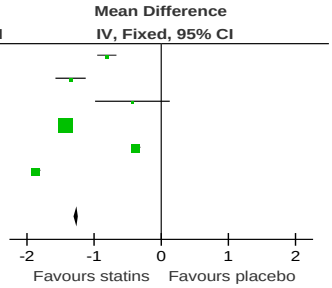


Studies in ascending order according to baseline LDL-cholesterol value

Figure 87: LDL-cholesterol (mmol/l): high intensity statin studies ranked according to baseline LDL-cholesterol

Study or Subgroup	Statins Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sola 2006	2.4	0.23	54	3.21	0.44	54	4.3%	-0.81 [-0.94, -0.68]
Terry 2007 CATZ	1.91	0.49	40	3.26	0.49	40	1.6%	-1.35 [-1.56, -1.14]
Lemos 2013	2.02742	1.15336	22	2.4567	0.700806	29	0.3%	-0.43 [-0.97, 0.12]
Amarenco 2006 SPARCL	1.89	0.62	2365	3.32	0.75	2366	48.8%	-1.43 [-1.47, -1.39]
Koren 2004 ALLIANCE	2.46	0.7	1146	2.84	0.7	1125	22.6%	-0.38 [-0.44, -0.32]
Athyros 2002 GREACE	2.5	0.1	800	4.37	0.83	800	22.4%	-1.87 [-1.93, -1.81]
Total (95% CI)			**4427**			**4414**	**100.0%**	**-1.26 [-1.29, -1.23]**

Heterogeneity: Chi² = 1449.28, df = 5 (P < 0.00001); I² = 100%
Test for overall effect: Z = 90.15 (P < 0.00001)



Studies in ascending order according to baseline LDL-cholesterol value

Figure 88: LDL-cholesterol (mmol/l): subgroup analysis according to statin drug/dose

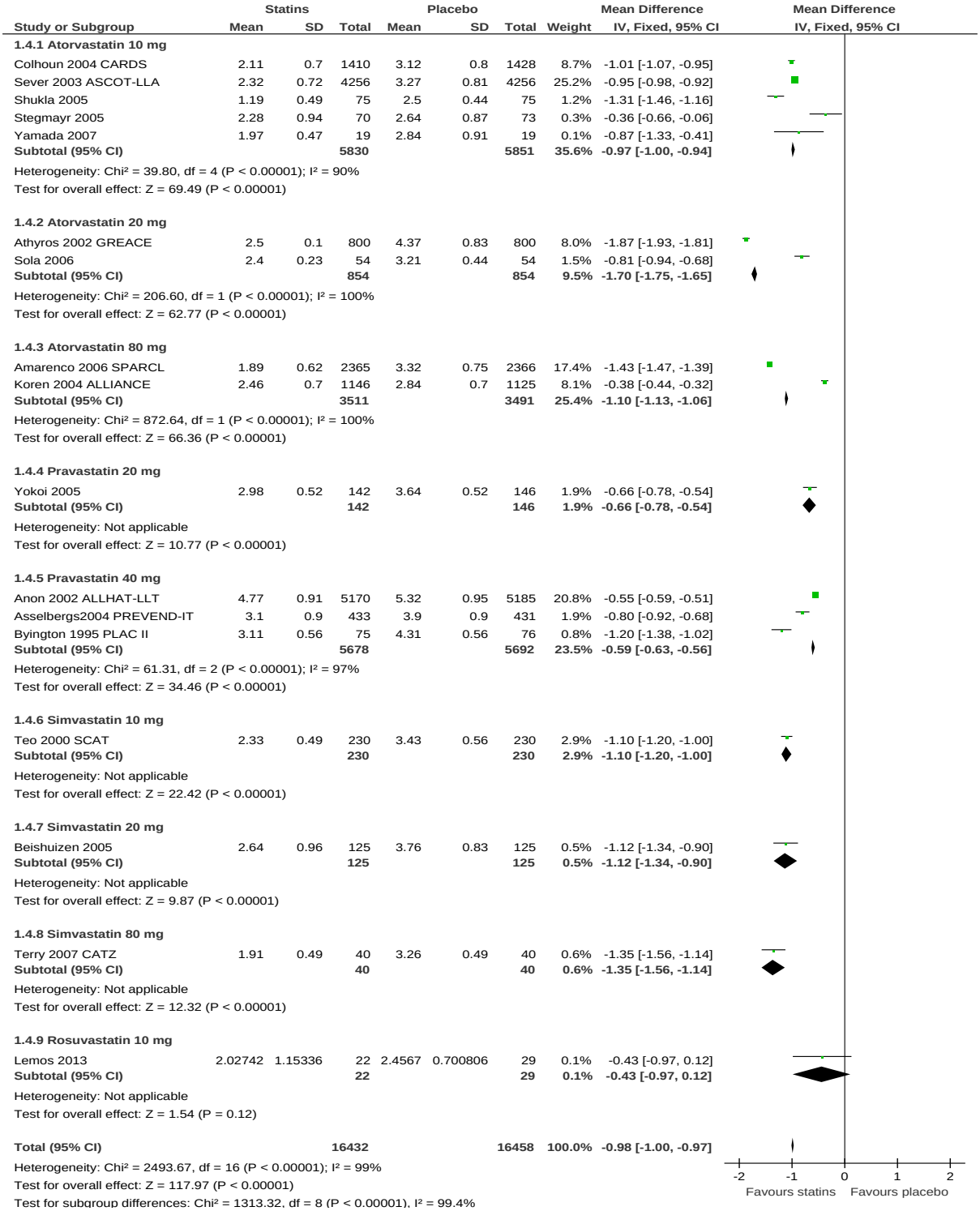


Figure 89: LDL-cholesterol reduction (mmol/l): subgroup analysis according to mean LDL-cholesterol reduction in statin arm

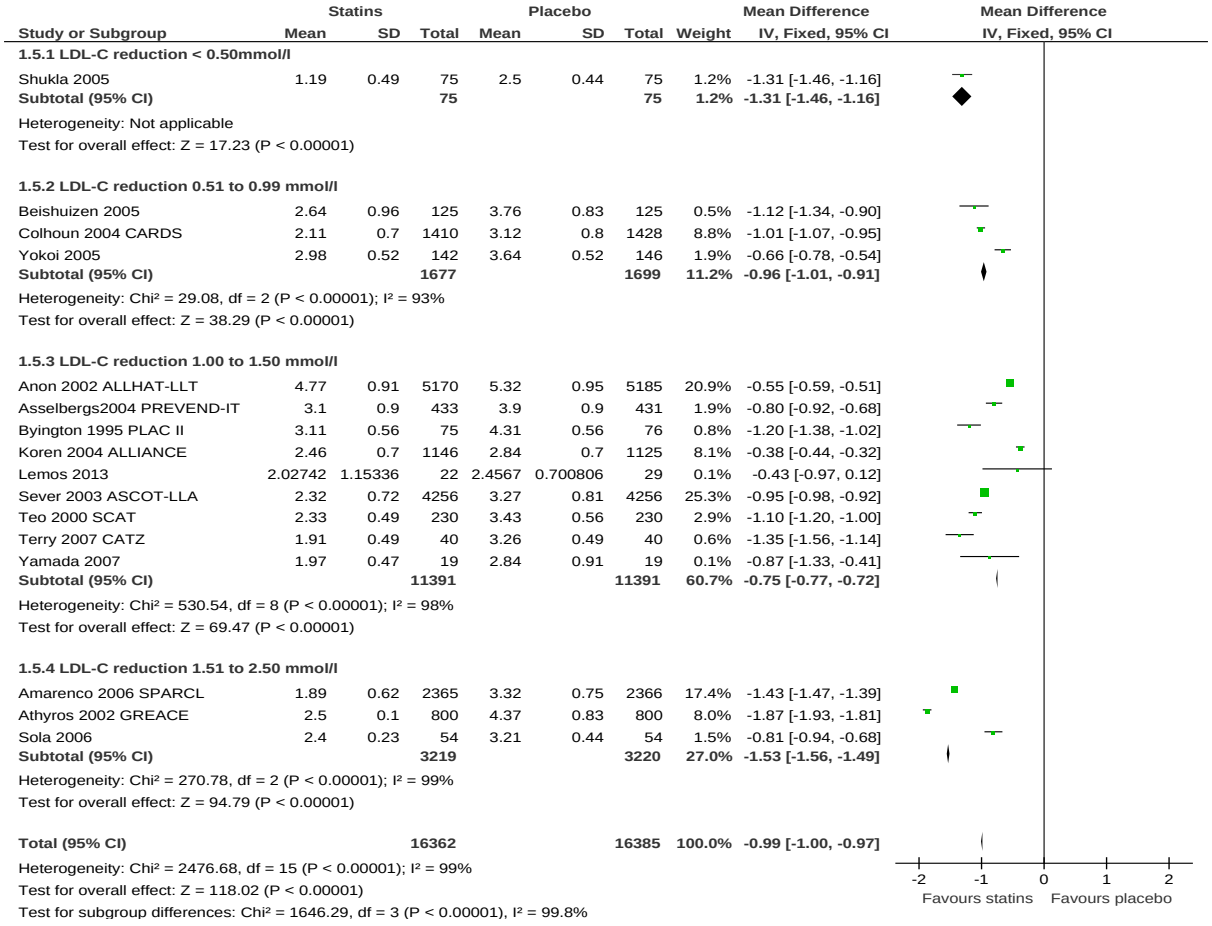
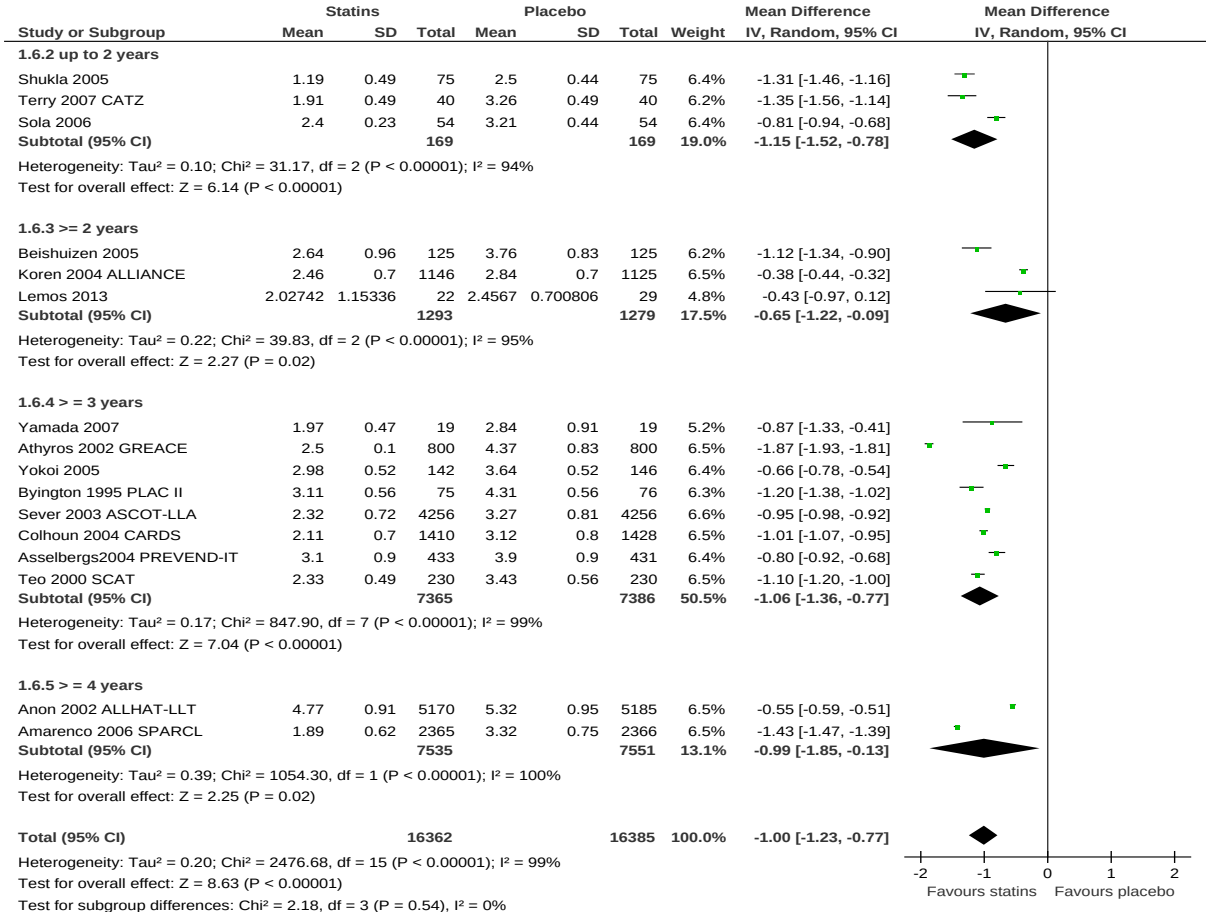


Figure 90: LDL-cholesterol reduction (mmol/l): subgroup analysis according to study follow-up time



I.4.8 High intensity statin (atorvastatin 80 mg) versus low intensity statin (pravastatin 40 mg)

Figure 91: All-cause mortality

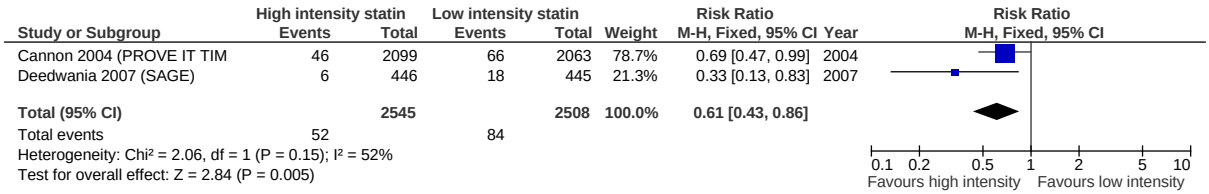


Figure 92: CV mortality

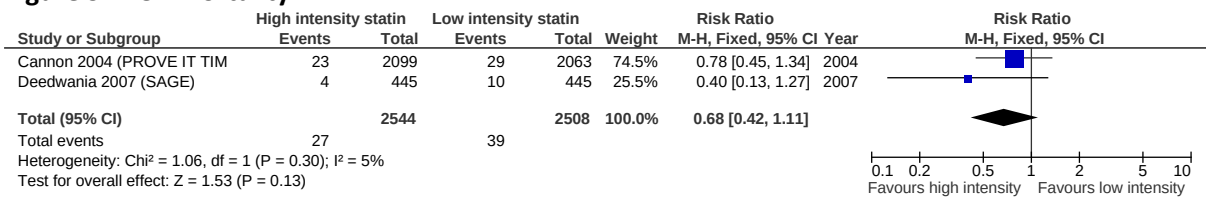


Figure 93: Non-fatal MI

Study or Subgroup	High intensity statin Events	Total	Low intensity statin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Cannon 2004 (PROVE IT TIM	139	2099	153	2063	100.0%	0.89 [0.72, 1.11]	2004
Total (95% CI)		**2099**		**2063**	**100.0%**	**0.89 [0.72, 1.11]**	
Total events	139		153				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

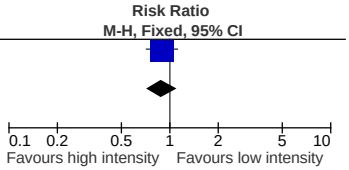


Figure 94: Stroke

Study or Subgroup	High intensity statin Events	Total	Low intensity statin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Cannon 2004 (PROVE IT TIM	21	2099	21	2063	87.6%	0.98 [0.54, 1.79]	2004
Deedwania 2007 (SAGE)	1	446	3	445	12.4%	0.33 [0.03, 3.19]	2007
Total (95% CI)		**2545**		**2508**	**100.0%**	**0.90 [0.51, 1.60]**	
Total events	22		24				

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

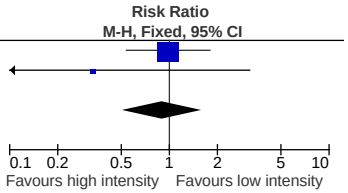


Figure 95: Adverse events: myalgia

Study or Subgroup	High intensity statin Events	Total	Low intensity statin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Deedwania 2007 (SAGE)	8	446	5	445	100.0%	1.60 [0.53, 4.84]	2007
Total (95% CI)		**446**		**445**	**100.0%**	**1.60 [0.53, 4.84]**	
Total events	8		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)

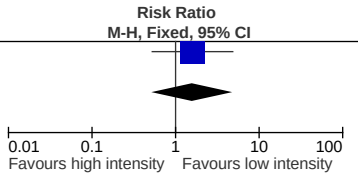


Figure 96: Rhabdomyolysis

Study or Subgroup	High intensity statin Events	Total	Low intensity statin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Cannon 2004 (PROVE IT TIM	0	2099	0	2063		Not estimable	2004
Raggi 2005	7	218	0	257	23.4%	17.67 [1.02, 307.65]	2005
Deedwania 2007 (SAGE)	0	446	1	445	76.6%	0.33 [0.01, 8.14]	2007
Total (95% CI)		**2763**		**2765**	**100.0%**	**4.39 [0.98, 19.72]**	
Total events	7		1				

Heterogeneity: Chi² = 3.41, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.93 (P = 0.05)

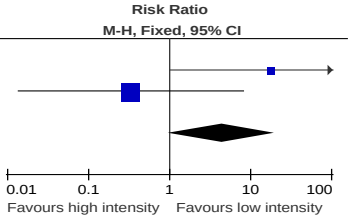
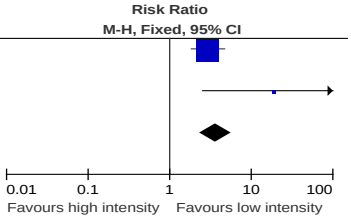


Figure 97: Adverse effects: liver adverse events (transaminases >3 x ULN)

Study or Subgroup	High intensity statin Events	Total	Low intensity statin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Cannon 2004 (PROVE IT TIM	69	2099	23	2063	95.9%	2.95 [1.85, 4.71]	2004
Raggi 2005	1	0	0	0		Not estimable	2005
Deedwania 2007 (SAGE)	19	446	1	445	4.1%	18.96 [2.55, 141.00]	2007
Total (95% CI)		**2545**		**2508**	**100.0%**	**3.61 [2.31, 5.65]**	
Total events	89		24				

Heterogeneity: Chi² = 3.34, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 5.62 (P < 0.00001)



I.4.9 High intensity statin (atorvastatin 80 mg or simvastatin 80 mg) versus medium intensity statin (atorvastatin 10 mg or simvastatin 20 mg)

Figure 98: All-cause mortality

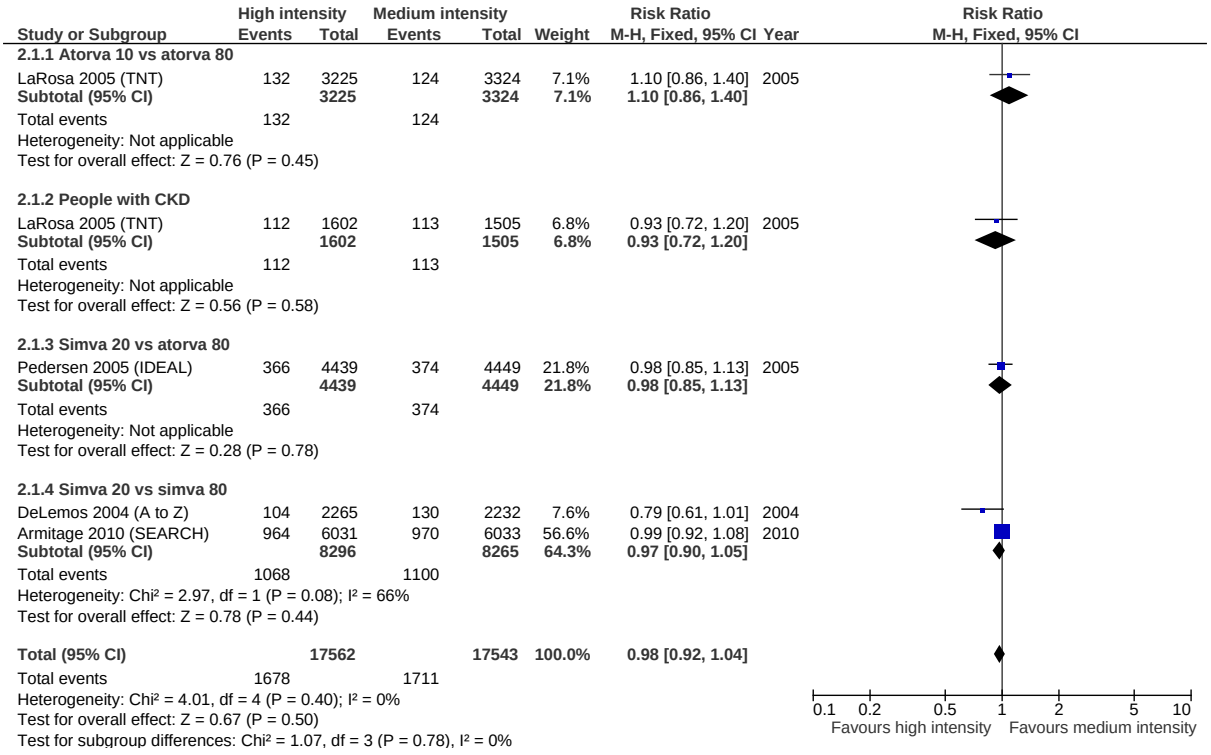


Figure 99: All-cause mortality: time to event

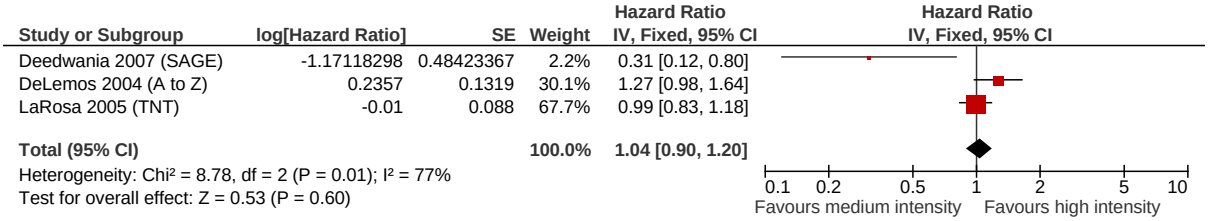


Figure 100: CV mortality

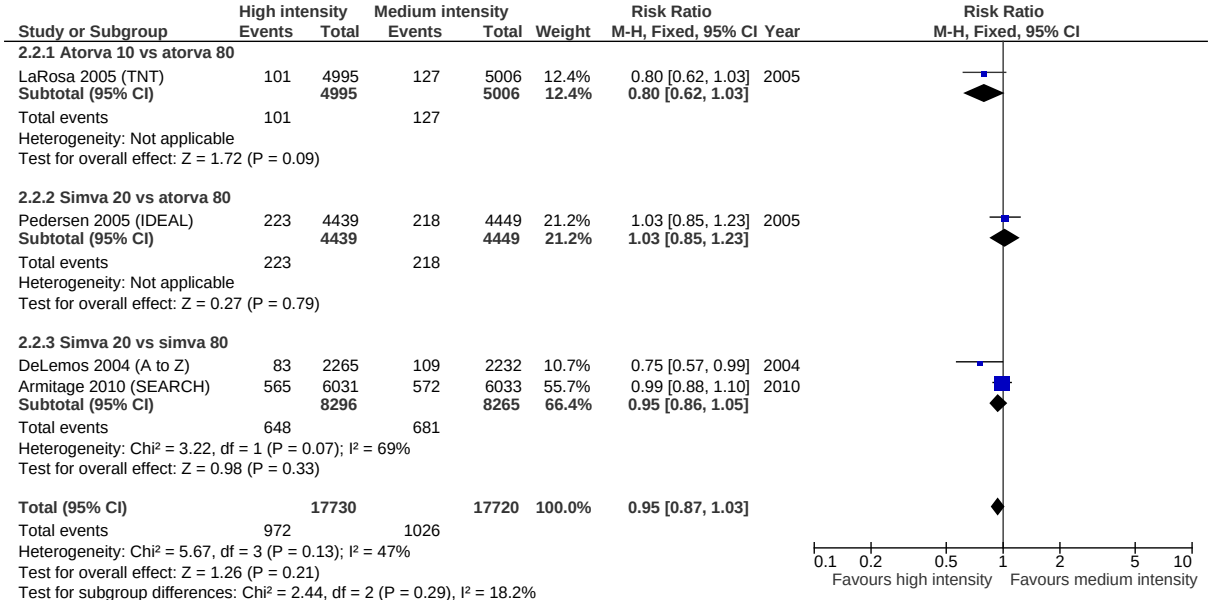


Figure 101: CV mortality: time to event

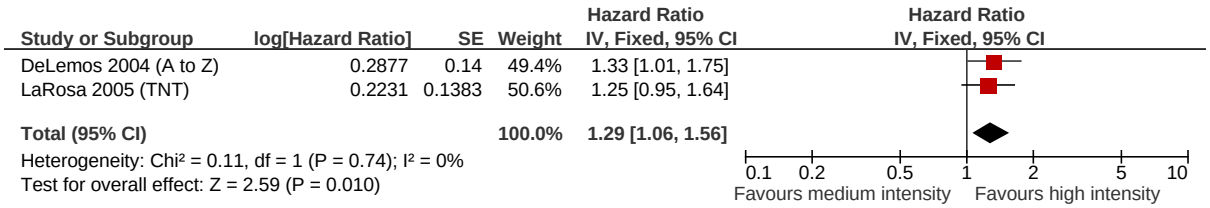


Figure 102: Non-fatal MI

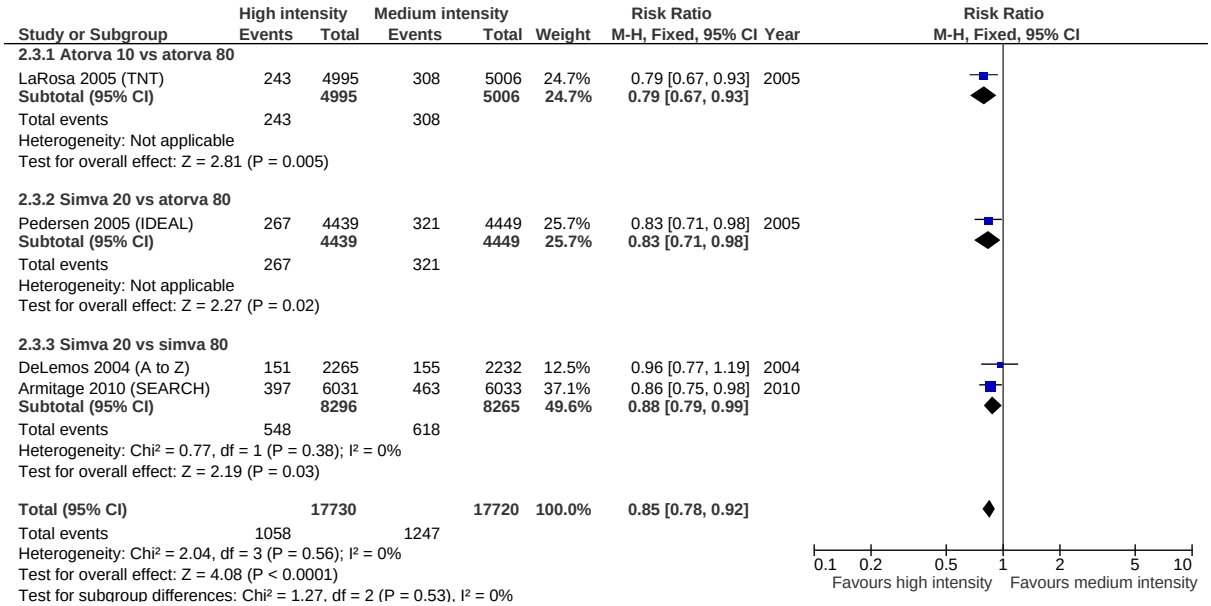


Figure 103: Stroke

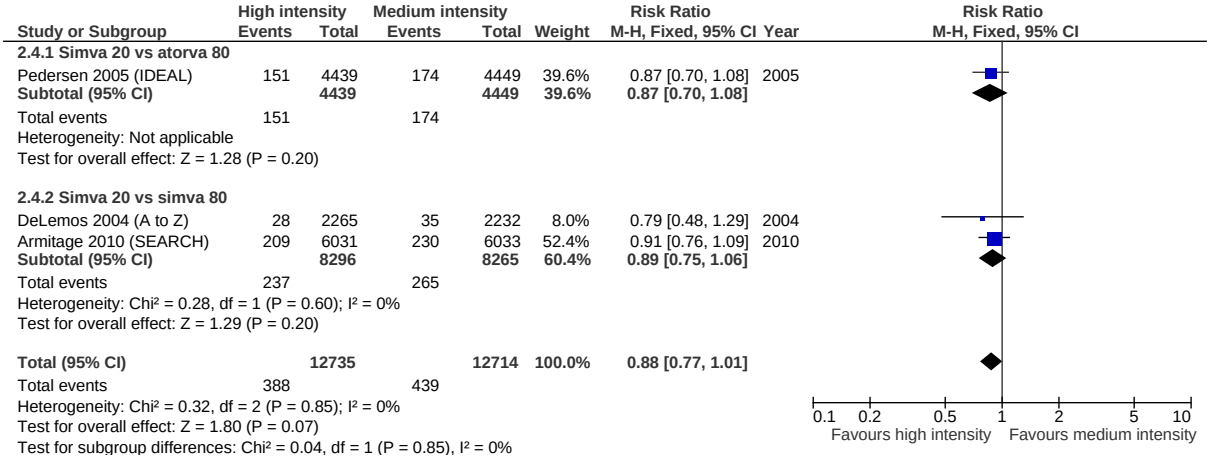


Figure 104: Adverse events: myalgia

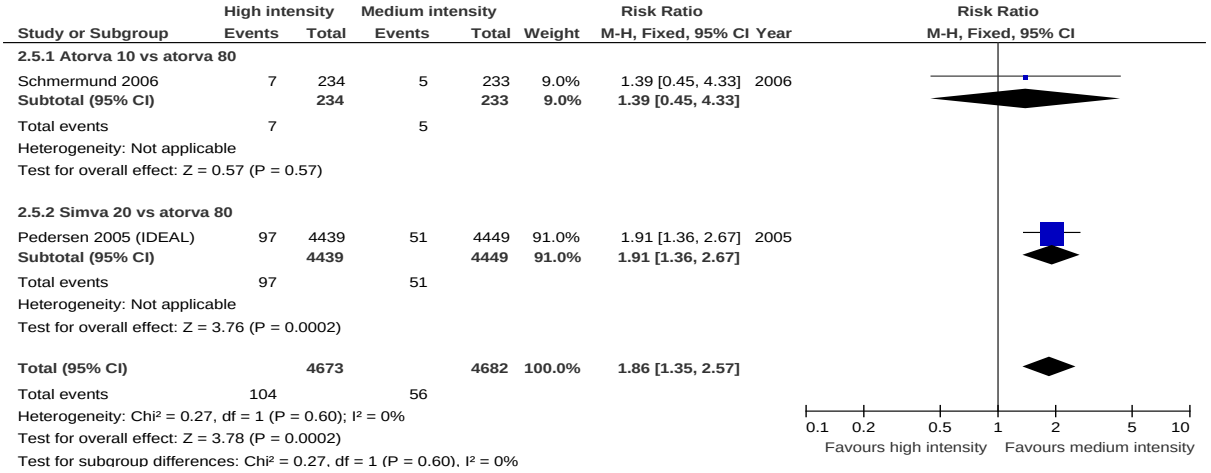


Figure 105: Adverse events: rhabdomyolysis

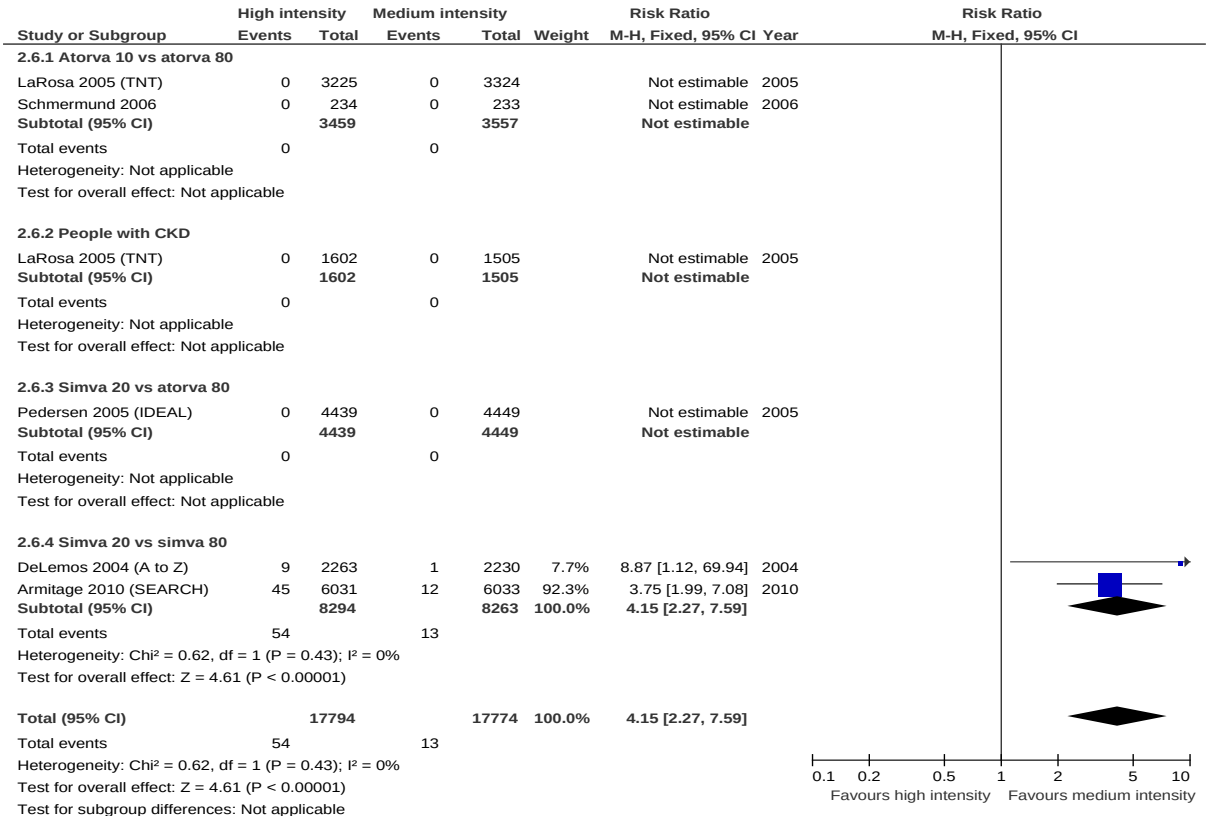


Figure 106: Adverse effects: liver adverse events (transaminases >3 x ULN)

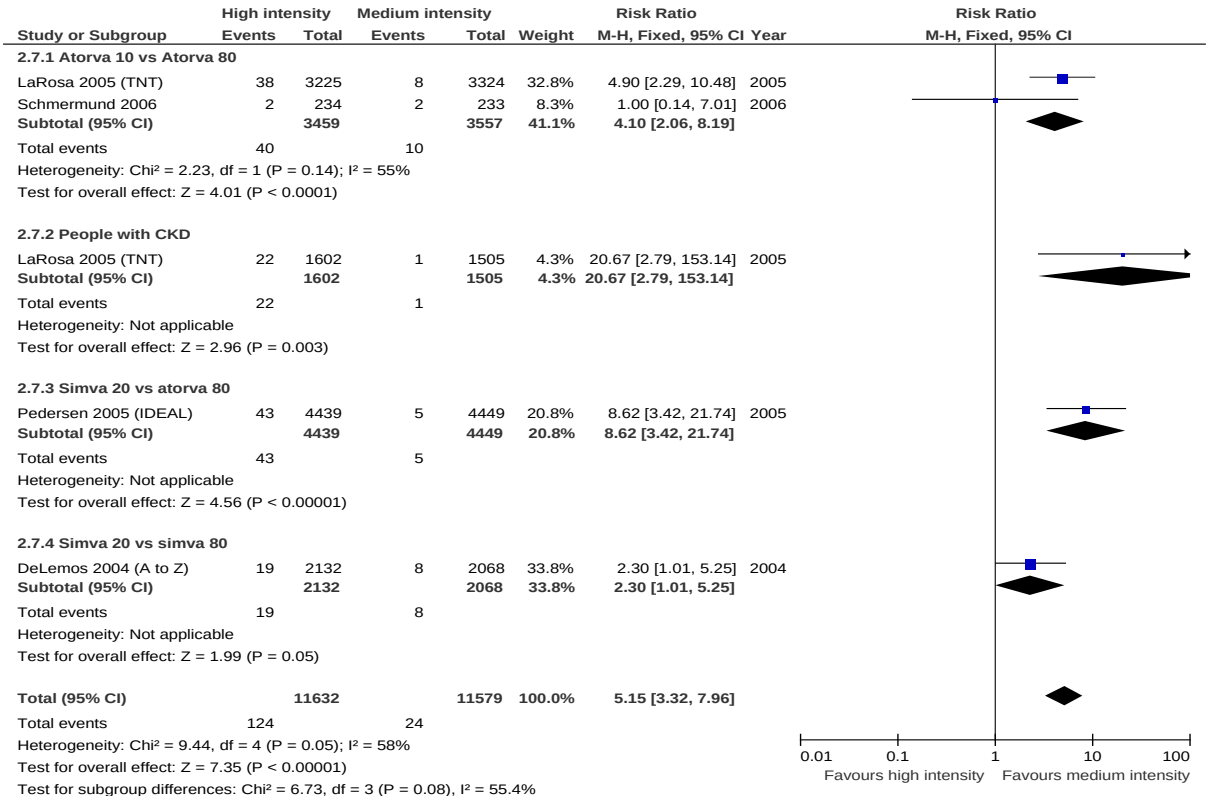
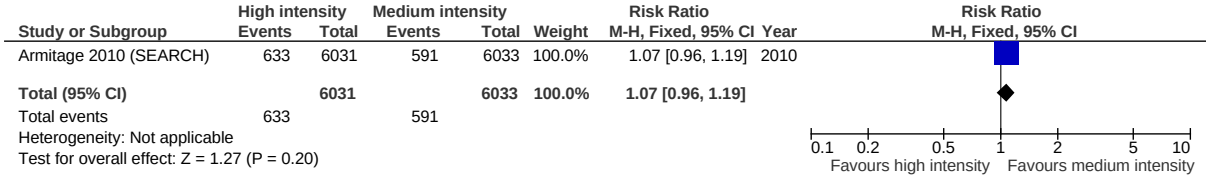


Figure 107: New-onset diabetes



I.4.10 Low intensity statin (simvastatin 10 mg) versus medium intensity statin (simvastatin 20 mg) for secondary prevention of CVD

Figure 108: CV mortality

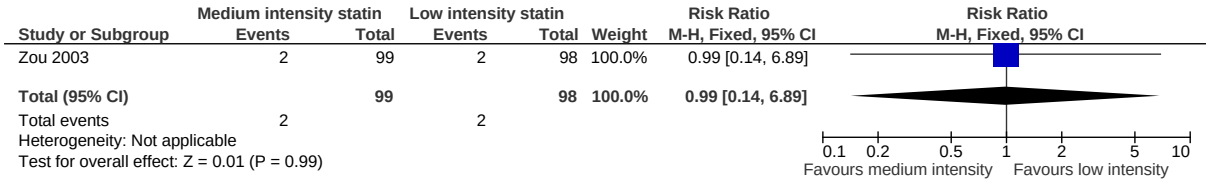
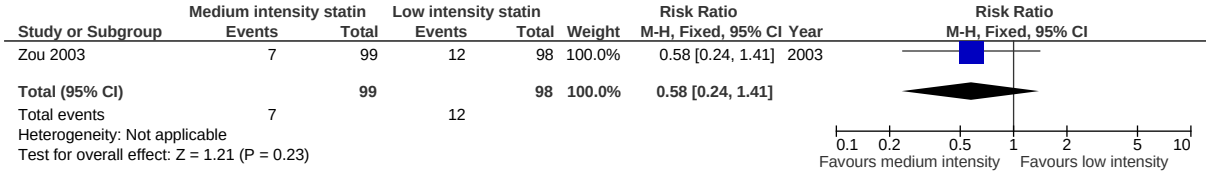


Figure 109: Non-fatal MI



I.4.11 Low intensity statin (simvastatin 10 mg or pravastatin 40 mg) versus medium or high intensity statin (simvastatin 20 mg or atorvastatin 80 mg) for secondary prevention of CVD

Figure 110: CV mortality

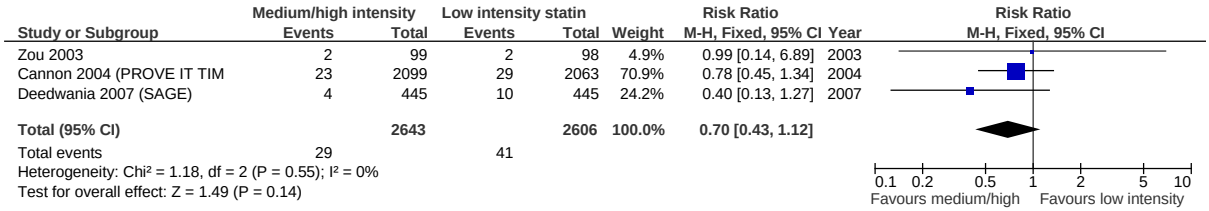
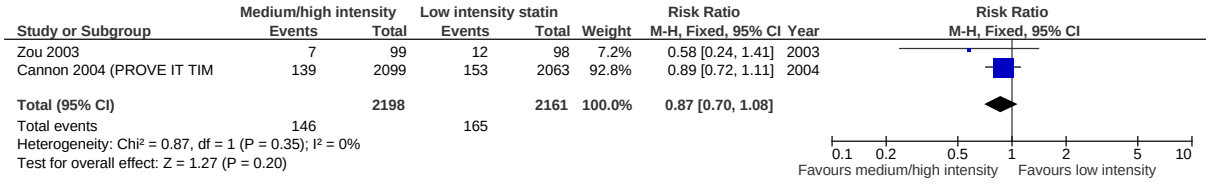


Figure 111: Non-fatal MI



I.4.12 Low intensity statin (pravastatin 5 mg) versus low intensity statin (pravastatin 10–20 mg) for secondary prevention of CVD

Figure 112: All-cause mortality

Study or Subgroup	Pravastatin 5 Events	Total	Pravastatin 20 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Ito 2001 (PATE)	20	334	14	331	100.0%	1.42 [0.73, 2.76]	2001
Total (95% CI)		**334**		**331**	**100.0%**	**1.42 [0.73, 2.76]**	
Total events	20		14				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)

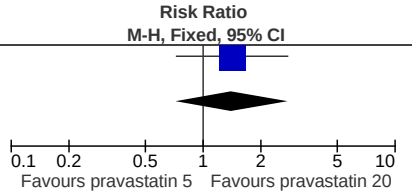


Figure 113: CV mortality

Study or Subgroup	Pravastatin 5 Events	Total	Pravastatin 20 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ito 2001 (PATE)	6	334	8	331	100.0%	0.74 [0.26, 2.12]
Total (95% CI)		**334**		**331**	**100.0%**	**0.74 [0.26, 2.12]**
Total events	6		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)

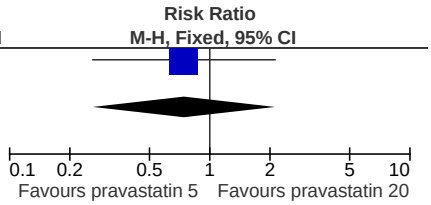
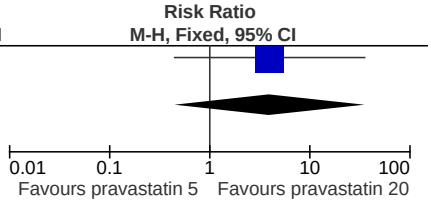


Figure 114: Non-fatal MI

Study or Subgroup	Pravastatin 5 Events	Total	Pravastatin 20 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ito 2001 (PATE)	4	334	1	331	100.0%	3.96 [0.45, 35.28]
Total (95% CI)		**334**		**331**	**100.0%**	**3.96 [0.45, 35.28]**
Total events	4		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)



I.4.13 High intensity statin (atorvastatin 80 mg) versus high intensity statin (rosuvastatin 40 mg) for secondary prevention of CVD

Figure 115: CV mortality

Study or Subgroup	Atorvastatin 80 Events	Total	Rosuvastatin 40 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Nicholls 2011 (SATURN)	2	689	2	691	100.0%	1.00 [0.14, 7.10]	2011
Total (95% CI)		**689**		**691**	**100.0%**	**1.00 [0.14, 7.10]**	
Total events	2		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

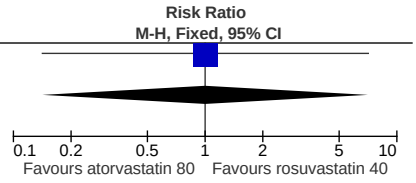


Figure 116: Non-fatal MI

Study or Subgroup	Atorvastatin 80 Events	Total	Rosuvastatin 40 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Nicholls 2011 (SATURN)	11	689	11	691	100.0%	1.00 [0.44, 2.30]	2011
Total (95% CI)		**689**		**691**	**100.0%**	**1.00 [0.44, 2.30]**	
Total events	11		11				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

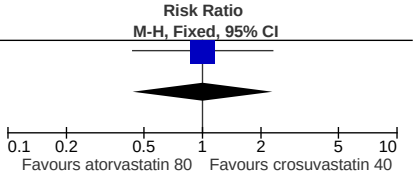


Figure 117: Stroke

Study or Subgroup	Atorvastatin 80 Events	Total	Rosuvastatin 40 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Nicholls 2011 (SATURN)	2	689	3	691	100.0%	0.67 [0.11, 3.99]	2011
Total (95% CI)		**689**		**691**	**100.0%**	**0.67 [0.11, 3.99]**	
Total events	2		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

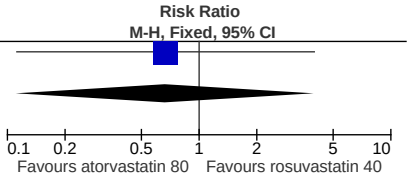


Figure 118: Adverse events: liver adverse events (transaminases >3 x ULN)

Study or Subgroup	Atorvastatin 80 Events	Total	Rosuvastatin 40 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Nicholls 2011 (SATURN)	14	668	5	668	100.0%	2.80 [1.01, 7.73]	2011
Total (95% CI)		**668**		**668**	**100.0%**	**2.80 [1.01, 7.73]**	
Total events	14		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)

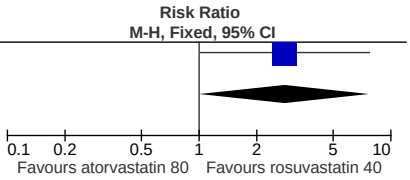


Figure 119: Adverse events: rhabdomyolysis

Study or Subgroup	Atorvastatin 40 Events	Total	Rosuvastatin 20 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
5.5.1 Atorvaostatin 80 mg vs rosuvastatin 40 mg							
Nicholls 2011 (SATURN)	4	668	1	668	100.0%	4.00 [0.45, 35.69]	2011
Subtotal (95% CI)		**668**		**668**	**100.0%**	**4.00 [0.45, 35.69]**	
Total events	4		1				

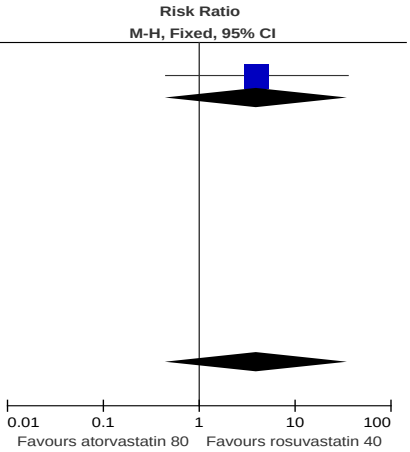
Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)

5.5.2 Atorvaostatin 40 mg vs rosuvastatin 20 mg							
Hong 2008	0	14	0	20		Not estimable	2008
Subtotal (95% CI)		**14**		**20**		**Not estimable**	
Total events	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable

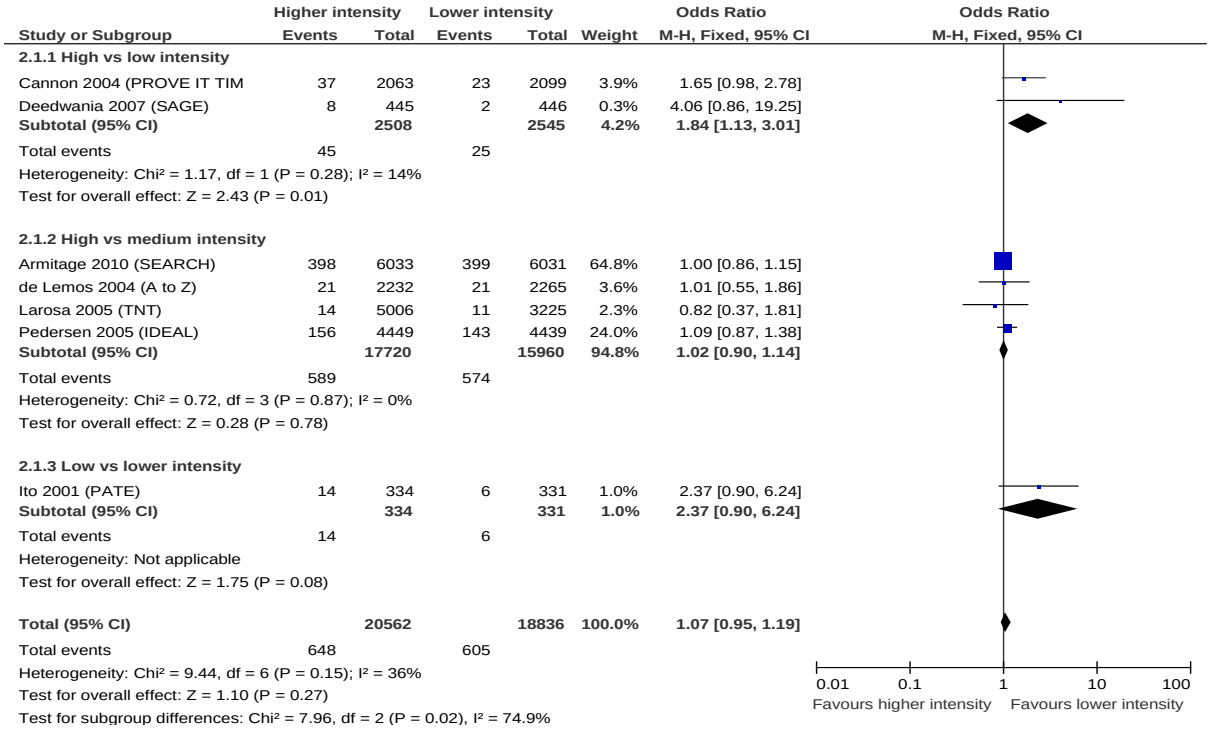
Total (95% CI)		**682**		**688**	**100.0%**	**4.00 [0.45, 35.69]**	
Total events	4		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable



I.4.14 Head-to-head statins: Non CVD mortality

Figure 120: Non CVD mortality: head-to-head studies by intensity



I.4.15 Head-to-head statins: LDL-cholesterol reduction

Figure 121: LDL-cholesterol (mmol/l): head-to-head studies combined

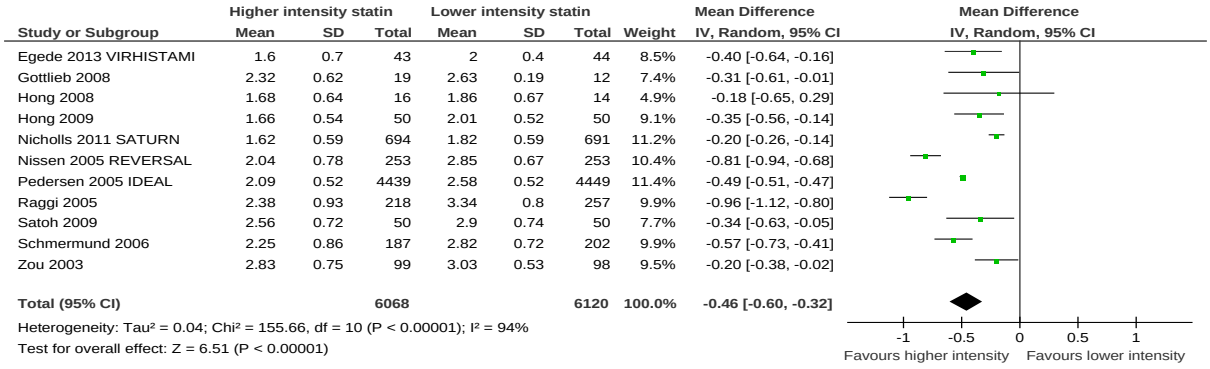


Figure 122: LDL-cholesterol (mmol/l): subgroup analysis according to statin intensity

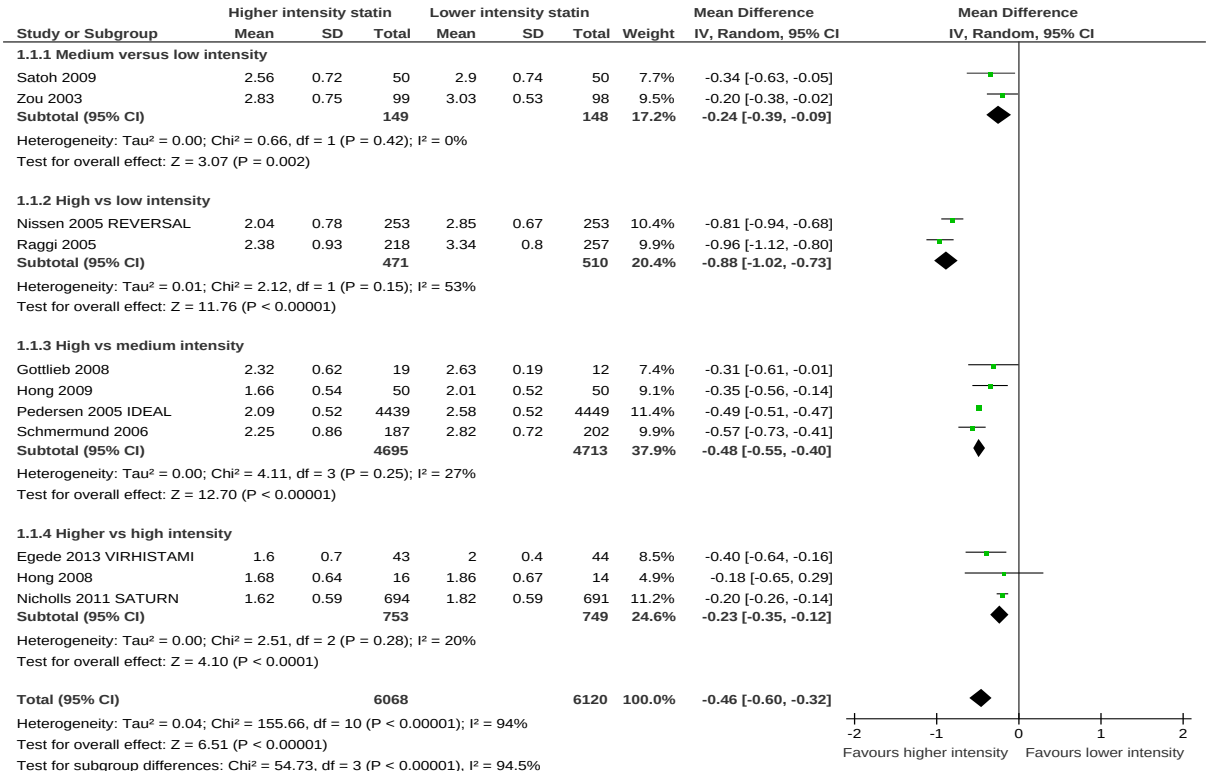
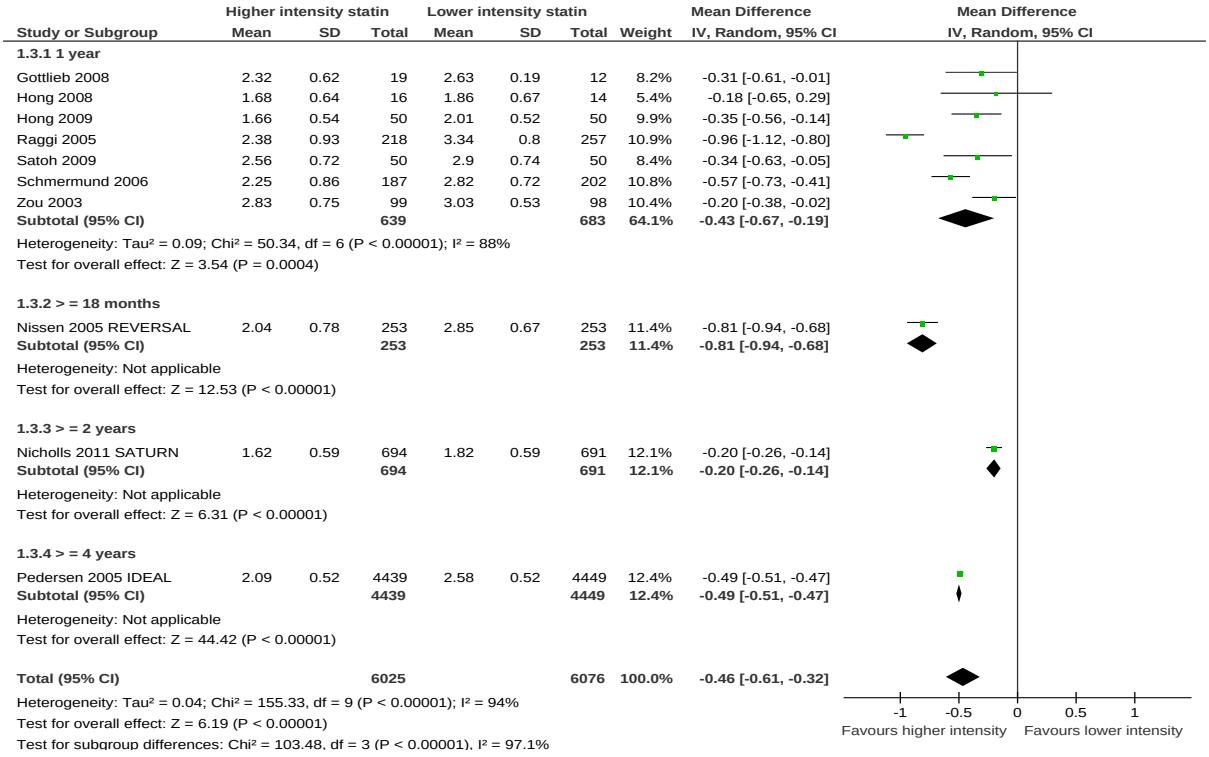


Figure 123: LDL-cholesterol reduction (mmol/l): subgroup analysis according to study follow-up time



I.5 Adherence to statin therapy

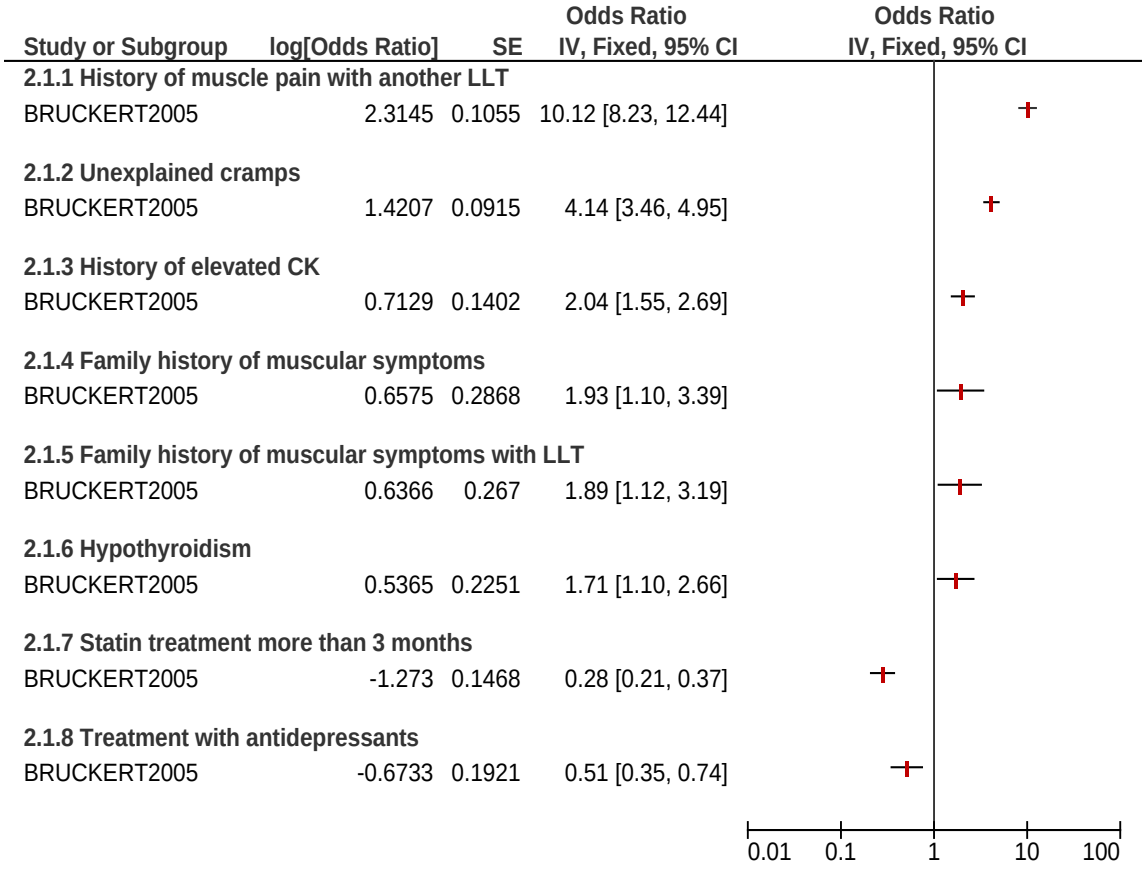
None

I.6 Statins: predictors of adverse events

I.6.1 Comparison: All patients on statin therapy

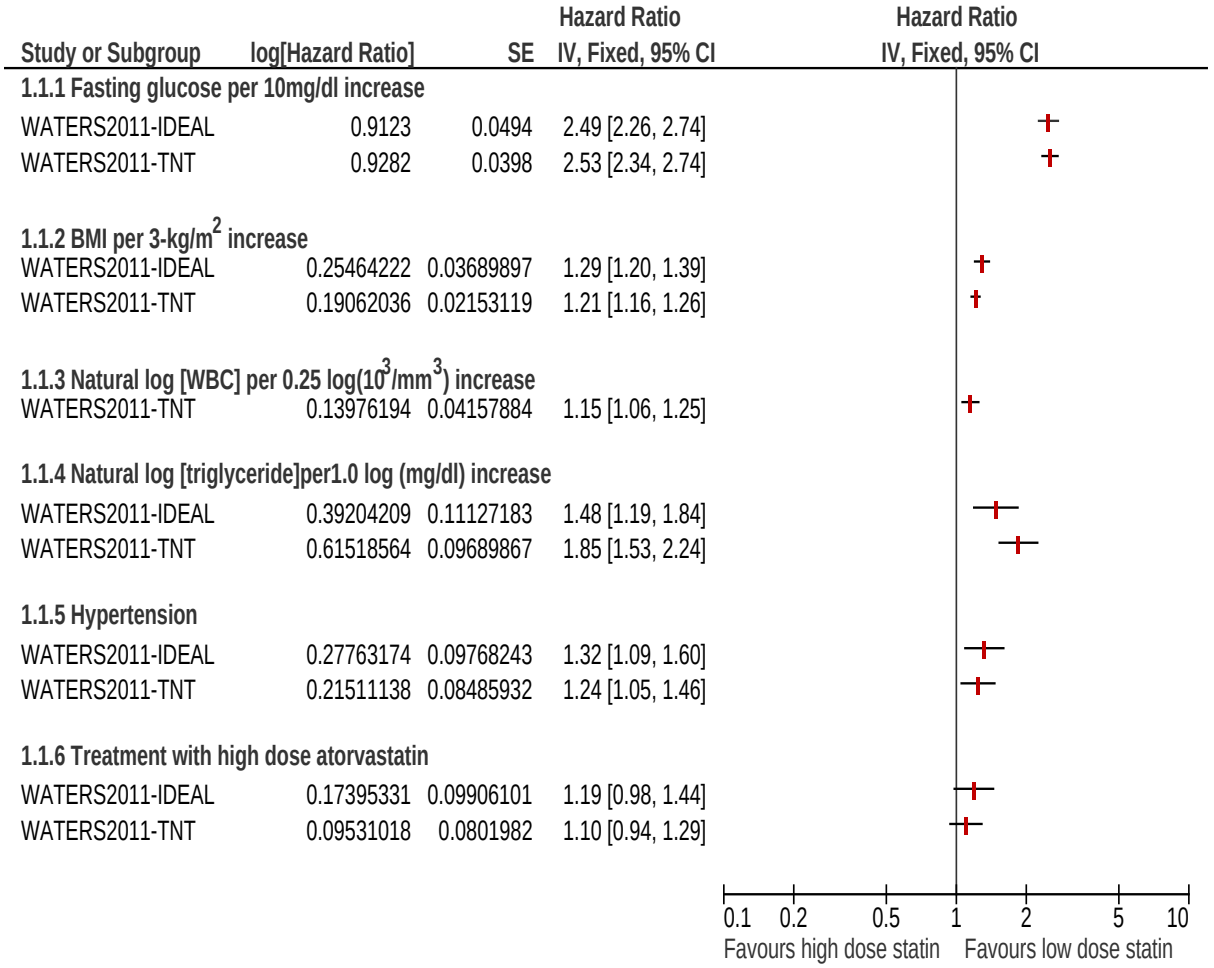
I.6.1.1 Outcome: Myalgia

Figure 124: Risk of myalgia in people on statin therapy



I.6.1.2 Outcome: New-onset diabetes

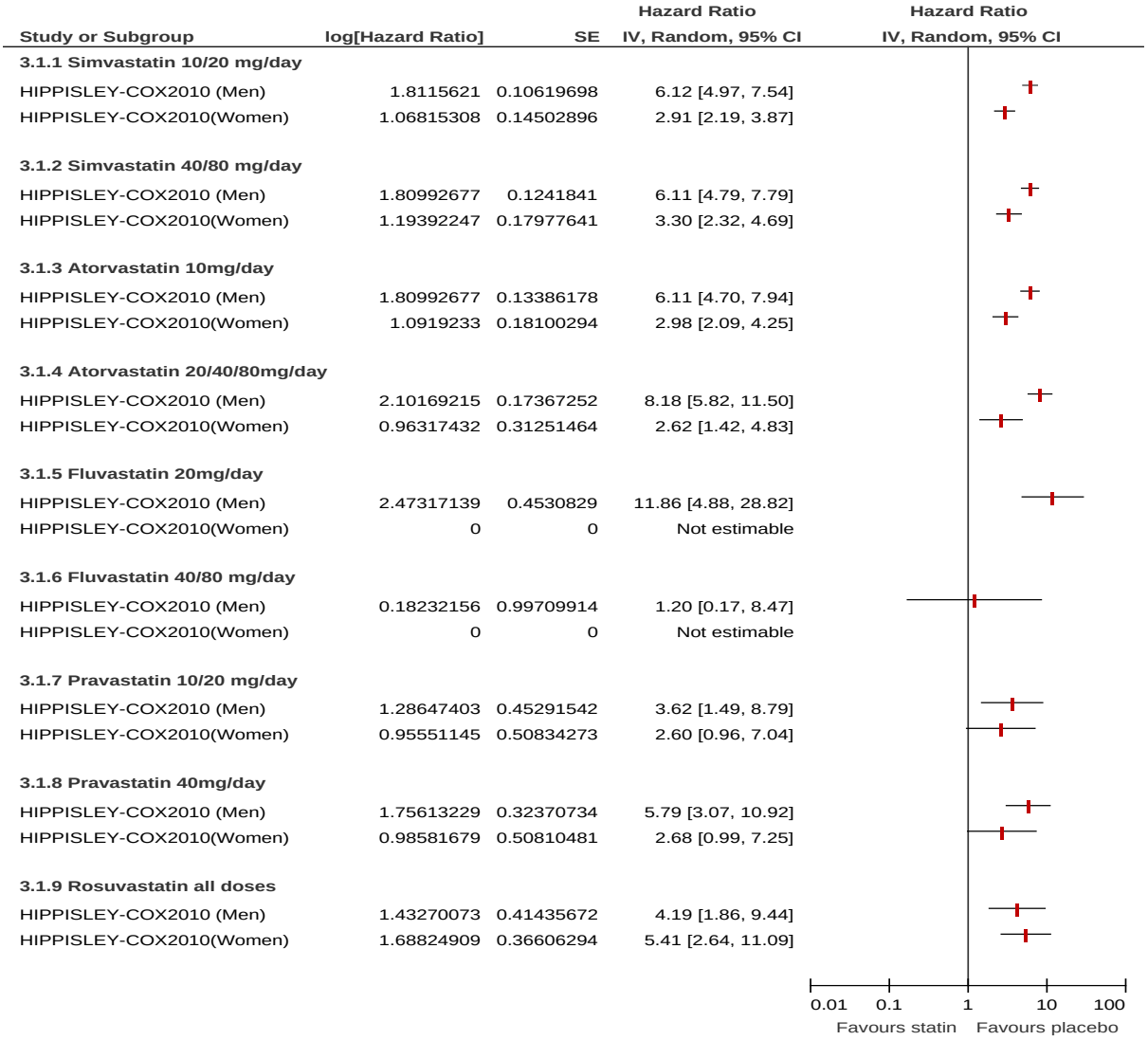
Figure 125: Risk of new-onset diabetes in people on statin therapy (high dose versus low dose)



I.7 Comparison: Statins versus placebo

I.7.1 Outcome: Rhabdomyolysis (myopathy)

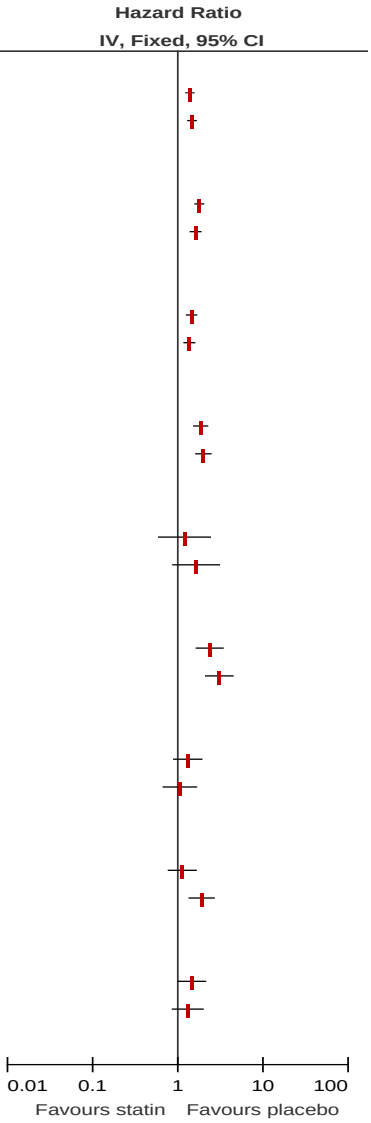
Figure 126: Risk of rhabdomyolysis in patients receiving statin therapy (by type and dose of statin)



I.7.1.1 Outcome: Liver transaminases more than 3 times normal level

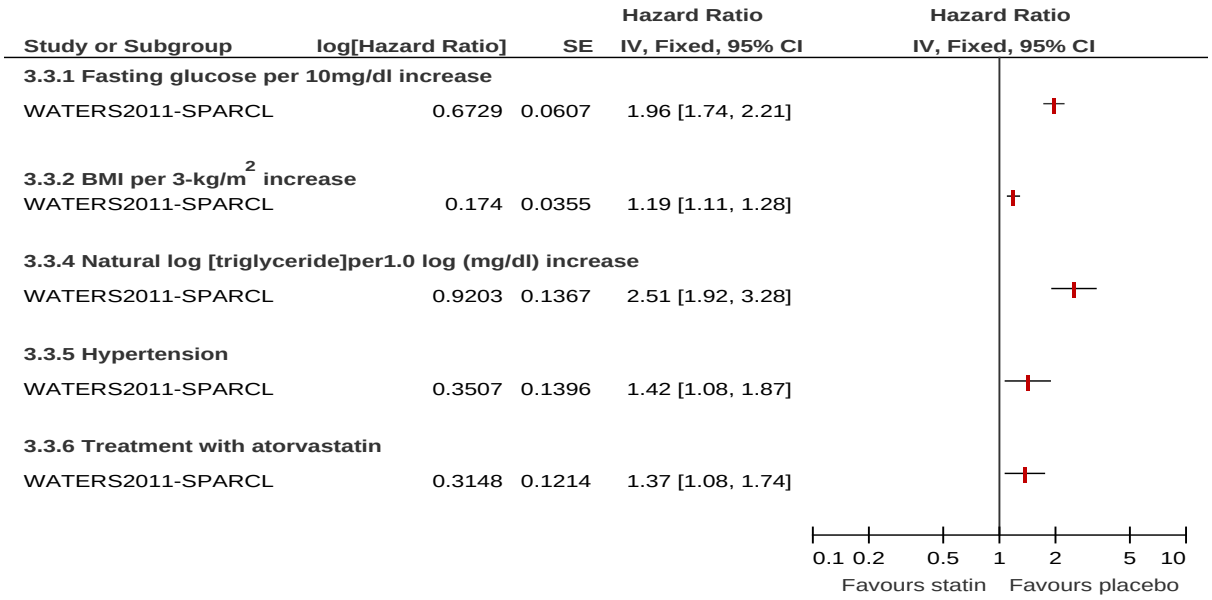
Figure 127: Risk of liver dysfunction in patients receiving statin therapy (by type and dose of statin)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
3.2.1 Simvastatin 10/20 mg/day			
HIPPISLEY-COX2010 (Men)	0.32930375	0.05416436	1.39 [1.25, 1.55]
HIPPISLEY-COX2010(Women)	0.3852624	0.05491461	1.47 [1.32, 1.64]
3.2.2 Simvastatin 40/80 mg/day			
HIPPISLEY-COX2010 (Men)	0.58221562	0.05725207	1.79 [1.60, 2.00]
HIPPISLEY-COX2010(Women)	0.48242615	0.07083622	1.62 [1.41, 1.86]
3.2.3 Atorvastatin 10mg/day			
HIPPISLEY-COX2010 (Men)	0.37156356	0.06762709	1.45 [1.27, 1.66]
HIPPISLEY-COX2010(Women)	0.31481074	0.07186736	1.37 [1.19, 1.58]
3.2.4 Atorvastatin 20/40/80mg/day			
HIPPISLEY-COX2010 (Men)	0.62057649	0.09302291	1.86 [1.55, 2.23]
HIPPISLEY-COX2010(Women)	0.69314718	0.10125234	2.00 [1.64, 2.44]
3.2.5 Fluvastatin 20mg/day			
HIPPISLEY-COX2010 (Men)	0.18232156	0.35365302	1.20 [0.60, 2.40]
HIPPISLEY-COX2010(Women)	0.49469624	0.31762299	1.64 [0.88, 3.06]
3.2.6 Fluvastatin 40/80 mg/day			
HIPPISLEY-COX2010 (Men)	0.86288996	0.18167291	2.37 [1.66, 3.38]
HIPPISLEY-COX2010(Women)	1.1249296	0.18578085	3.08 [2.14, 4.43]
3.2.7 Pravastatin 10/20 mg/day			
HIPPISLEY-COX2010 (Men)	0.27002714	0.19152783	1.31 [0.90, 1.91]
HIPPISLEY-COX2010(Women)	0.05826891	0.22649977	1.06 [0.68, 1.65]
3.2.8 Pravastatin 40mg/day			
HIPPISLEY-COX2010 (Men)	0.12221763	0.18912541	1.13 [0.78, 1.64]
HIPPISLEY-COX2010(Women)	0.64710324	0.16954011	1.91 [1.37, 2.66]
3.2.9 Rosuvastatin all doses			
HIPPISLEY-COX2010 (Men)	0.37843644	0.18800657	1.46 [1.01, 2.11]
HIPPISLEY-COX2010(Women)	0.27002714	0.20882486	1.31 [0.87, 1.97]



I.7.1.2 Outcome: New-onset diabetes

Figure 128: Risk of new-onset diabetes



I.8 Fibrates for prevention of CVD

Figure 129: All-cause mortality

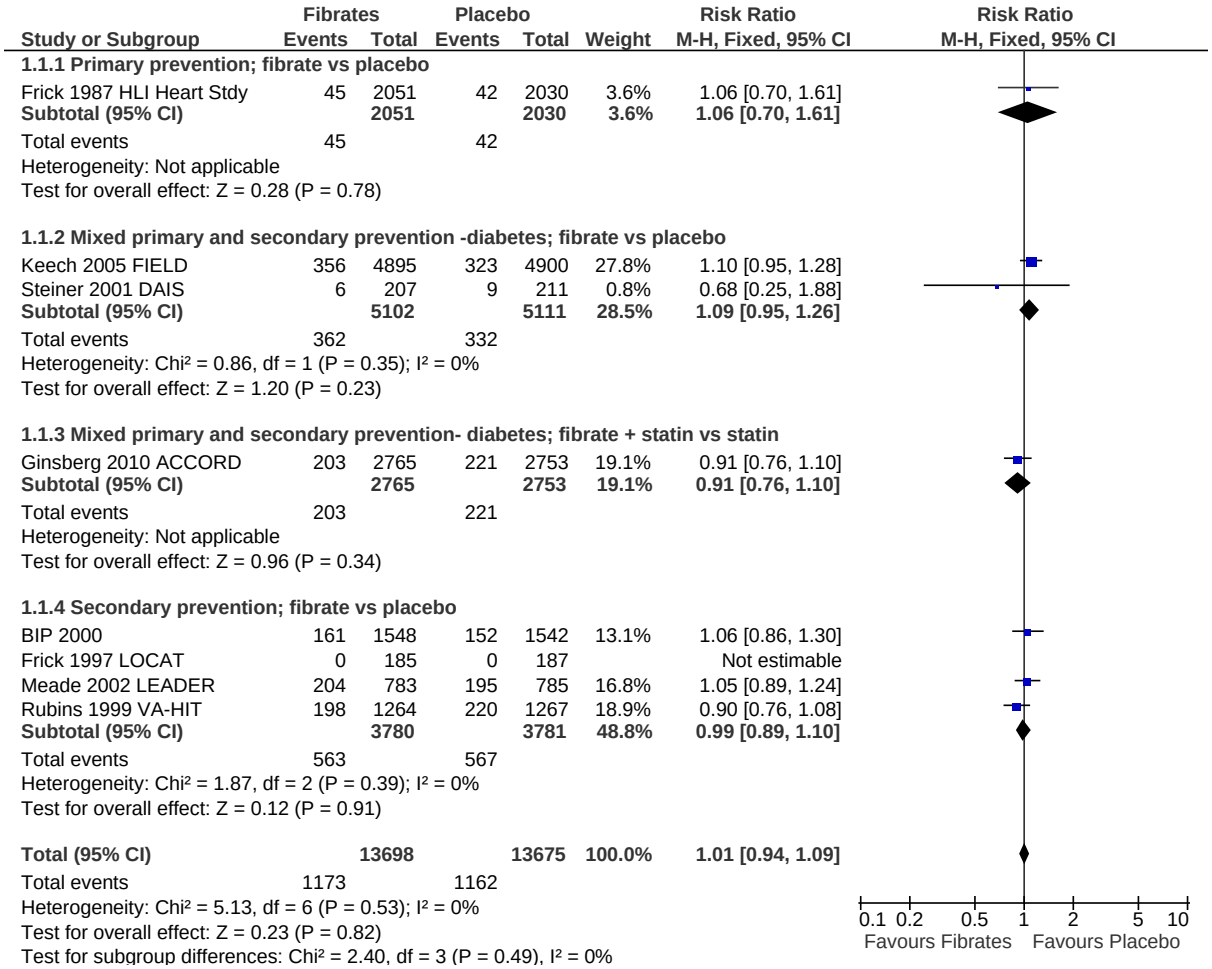


Figure 130: Cardiovascular mortality

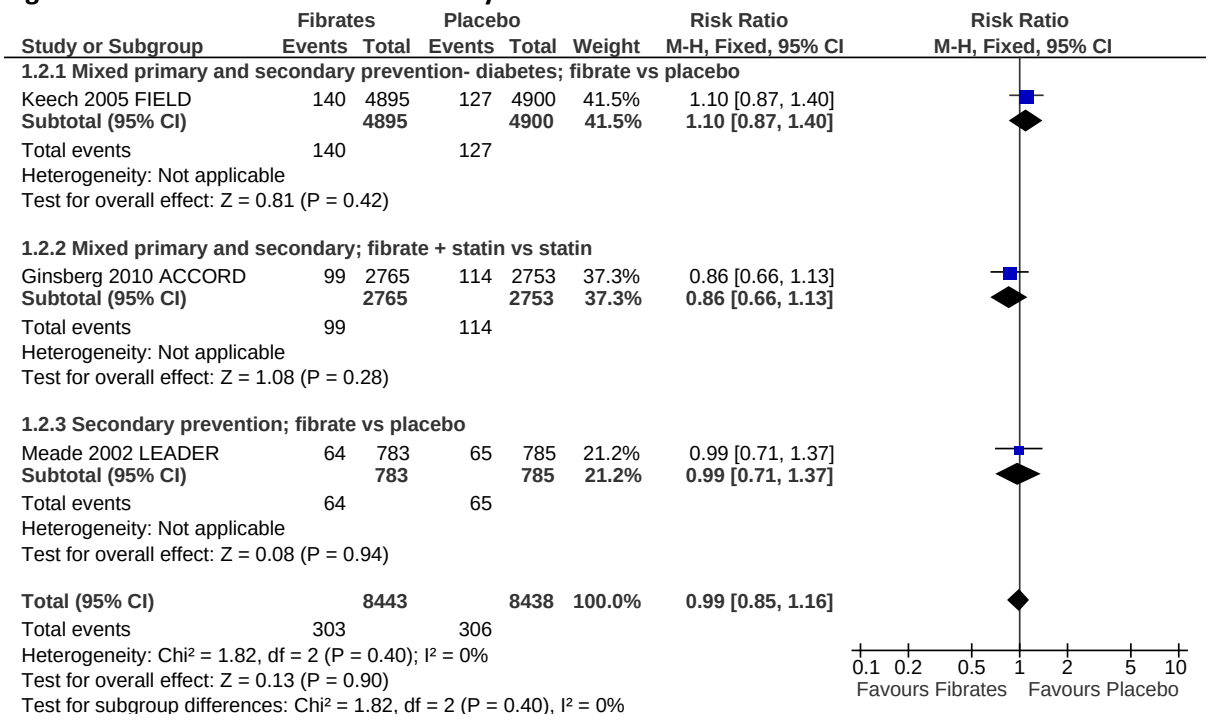


Figure 131: Non-fatal MI

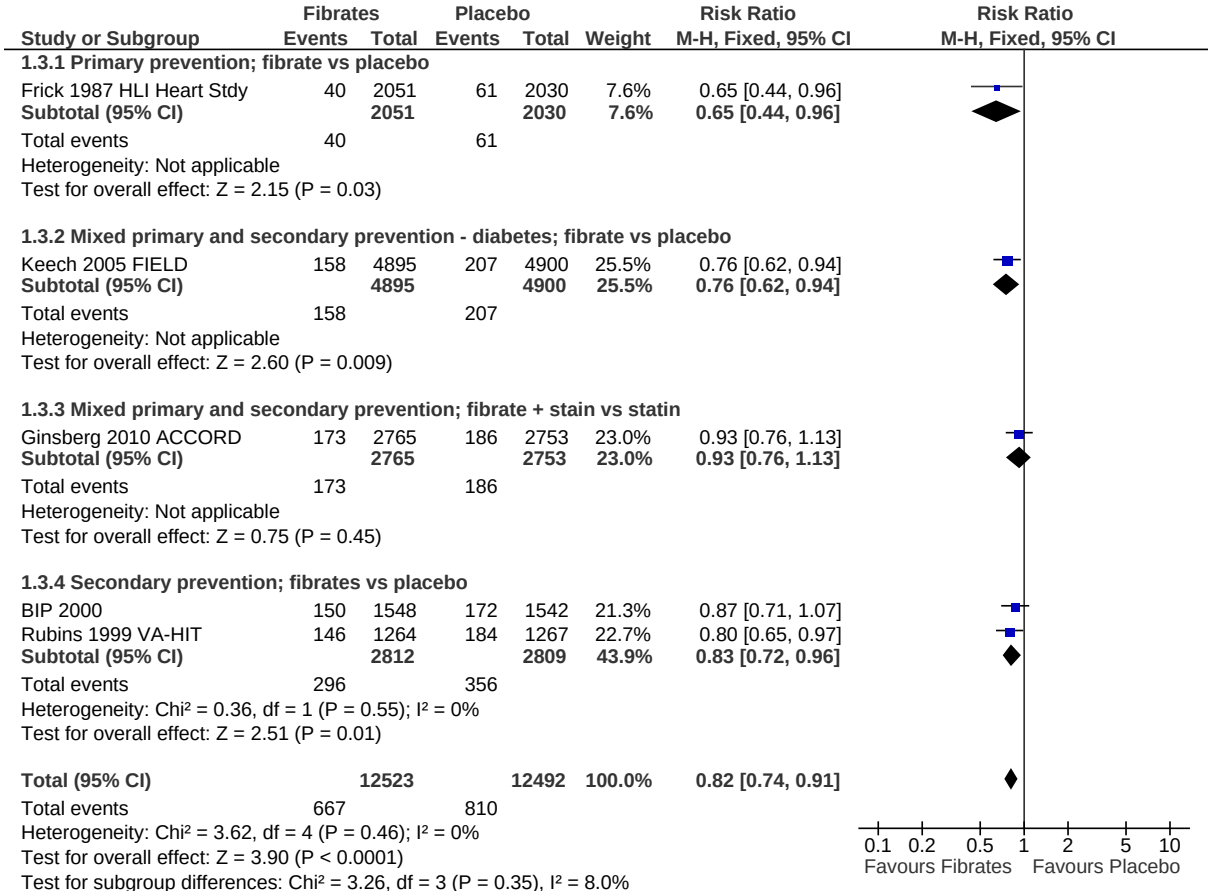


Figure 132: Sudden cardiac death

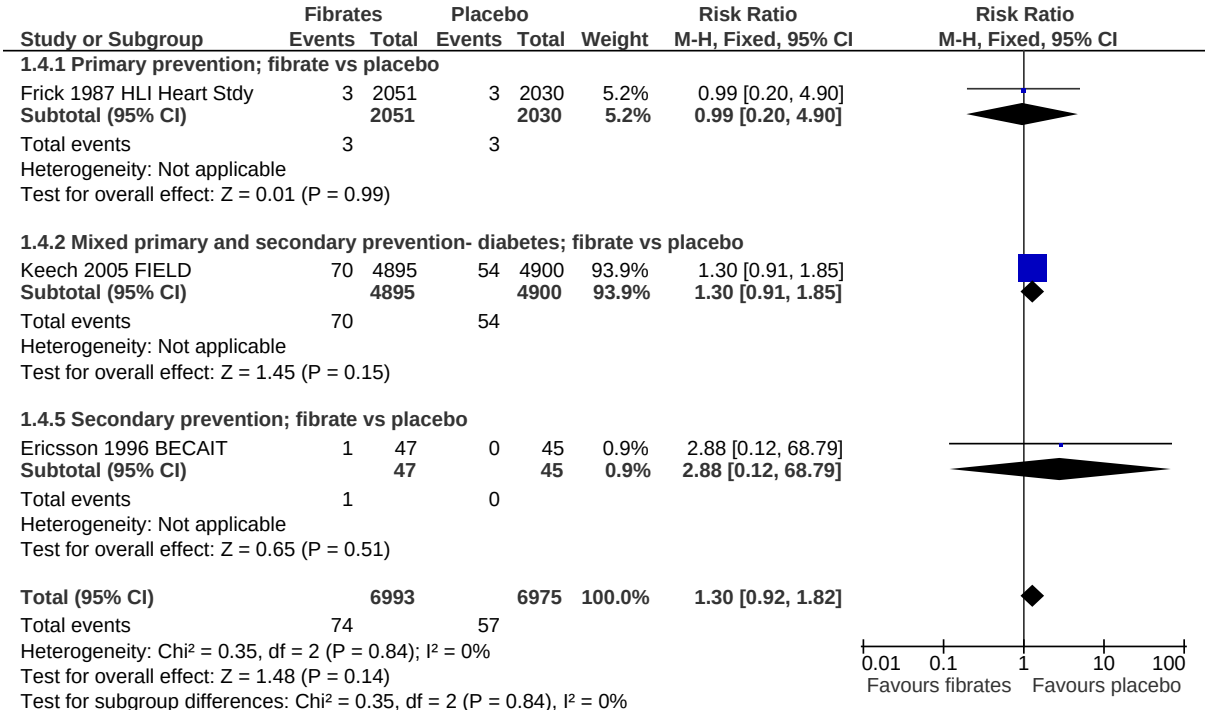


Figure 133: Stroke

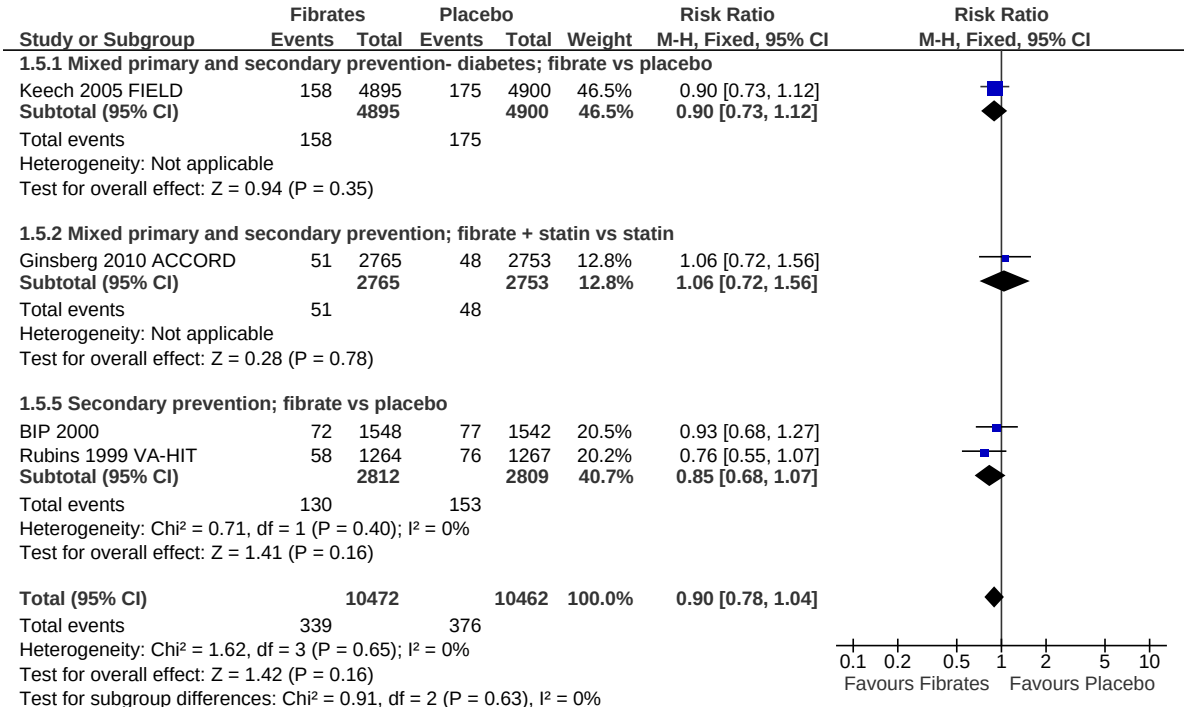


Figure 134: Hospitalisation

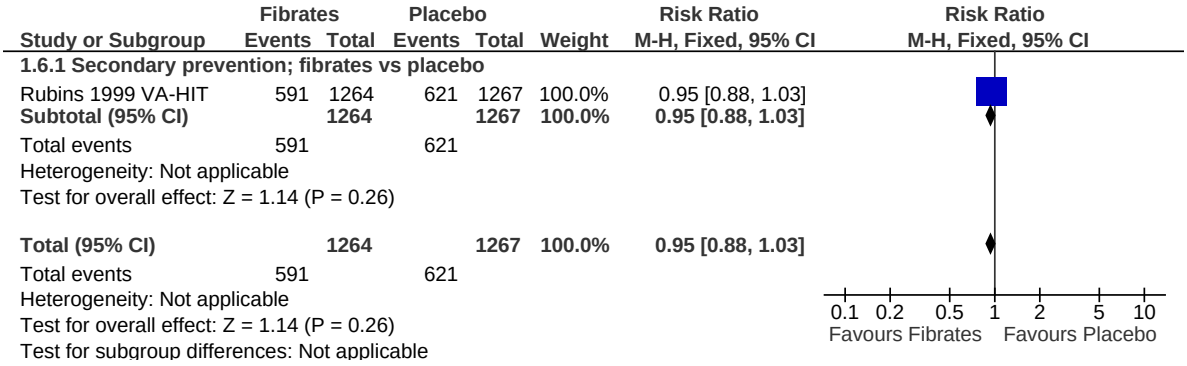


Figure 135: Raised alanine aminotransferase (more than 3 times the upper limit of normal)

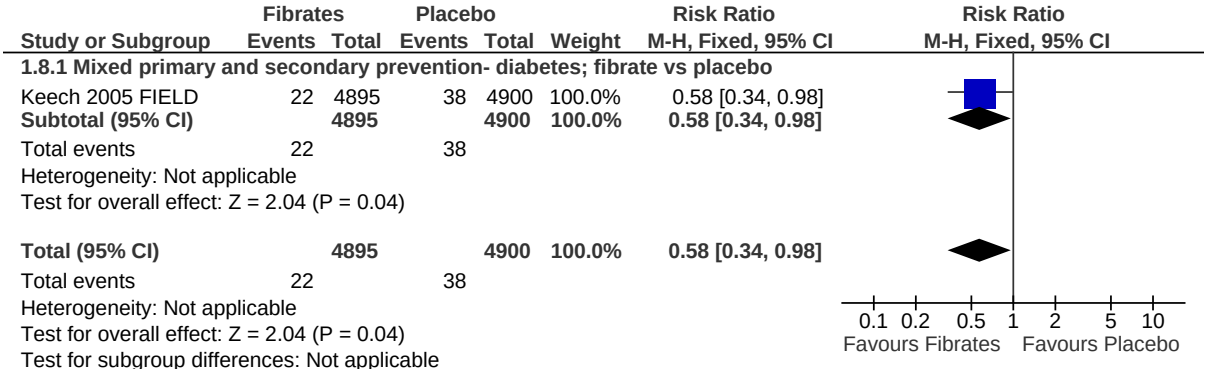
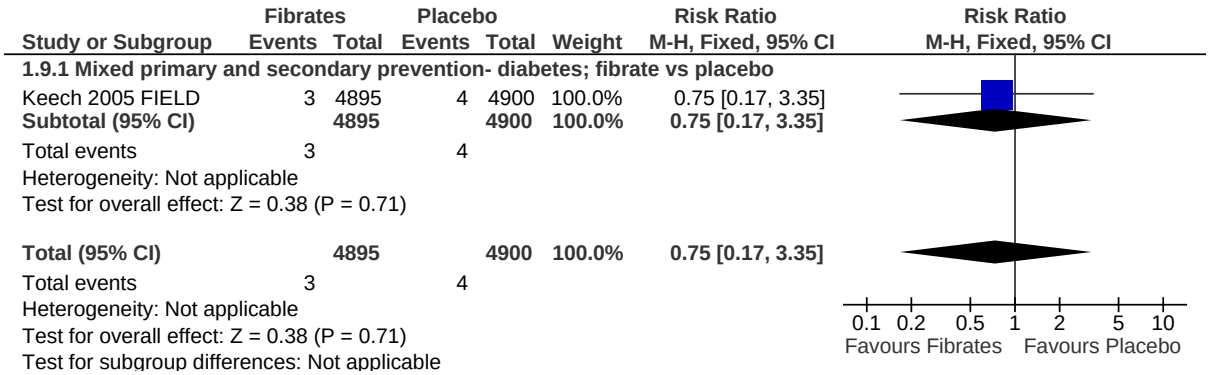


Figure 136: Raised creatine phosphokinase (more than 10 times the upper limit of normal)



I.9 Nicotinic acid for the prevention of CVD

Figure 137: All-cause mortality in secondary prevention

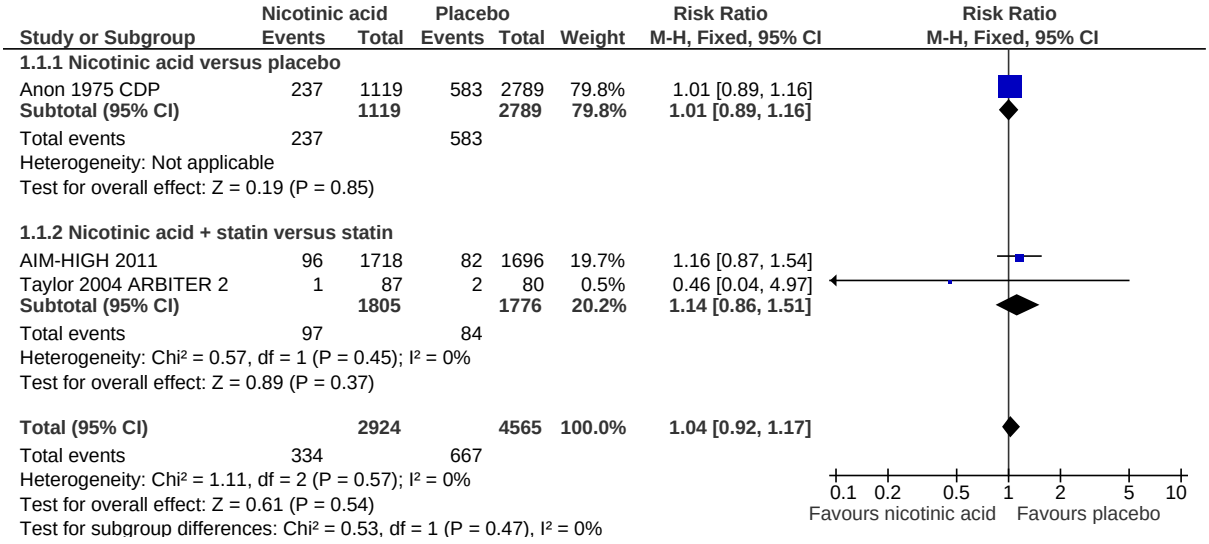


Figure 138: CV mortality in secondary prevention

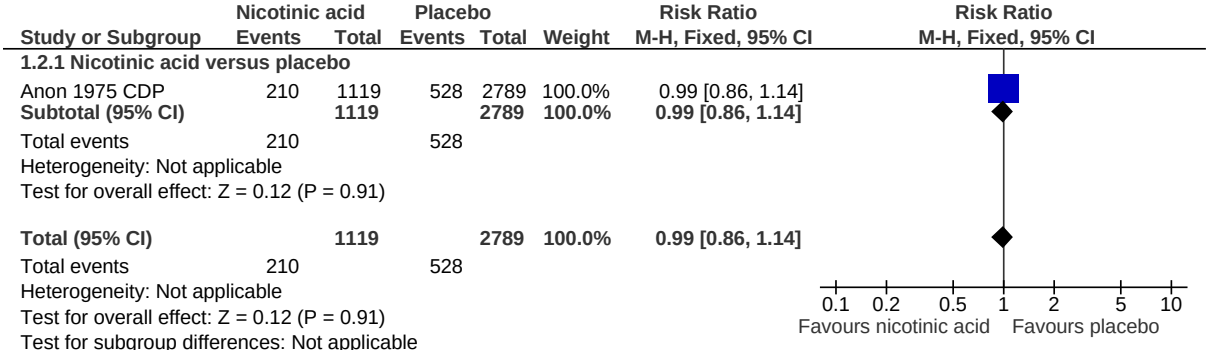


Figure 139: Non-fatal MI in secondary prevention

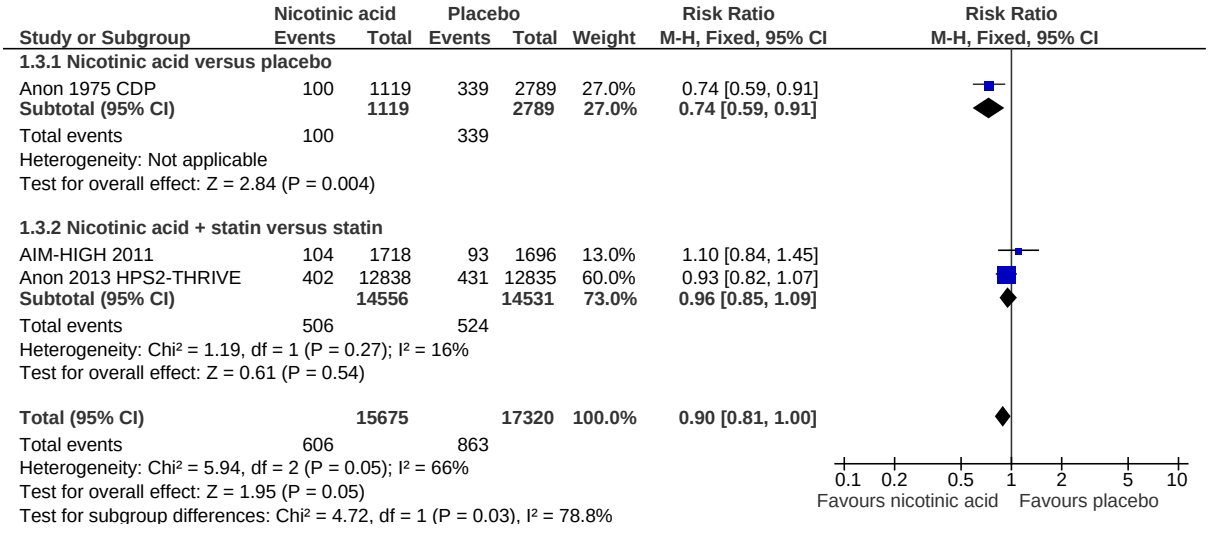


Figure 140: Sudden cardiac death in secondary prevention

Study or Subgroup	Nicotinic acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Nicotinic acid versus placebo						
Anon 1975 CDP	118	1119	269	2789	100.0%	1.09 [0.89, 1.34]
Subtotal (95% CI)		**1119**		**2789**	**100.0%**	**1.09 [0.89, 1.34]**
Total events	118		269			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
Total (95% CI)		**1119**		**2789**	**100.0%**	**1.09 [0.89, 1.34]**
Total events	118		269			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Not applicable						

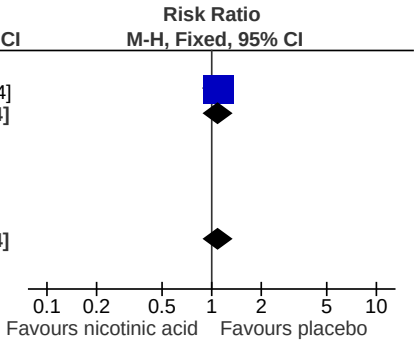


Figure 141: Stroke in secondary prevention

Study or Subgroup	Nicotinic acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Nicotinic acid versus placebo						
Anon 1975 CDP	86	1119	271	2789	23.0%	0.79 [0.63, 1.00]
Subtotal (95% CI)		**1119**		**2789**	**23.0%**	**0.79 [0.63, 1.00]**
Total events	86		271			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.98 (P = 0.05)						
1.5.2 Nicotinic acid + statin versus statin						
AIM-HIGH 2011	29	1718	18	1696	2.7%	1.59 [0.89, 2.85]
Anon 2013 HPS2-THRIVE	498	12838	499	12835	74.1%	1.00 [0.88, 1.13]
Taylor 2004 ARBITER 2	0	87	1	80	0.2%	0.31 [0.01, 7.42]
Subtotal (95% CI)		**14643**		**14611**	**77.0%**	**1.02 [0.90, 1.14]**
Total events	527		518			
Heterogeneity: Chi² = 2.89, df = 2 (P = 0.24); I² = 31%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**15762**		**17400**	**100.0%**	**0.96 [0.87, 1.07]**
Total events	613		789			
Heterogeneity: Chi² = 6.41, df = 3 (P = 0.09); I² = 53%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 3.54, df = 1 (P = 0.06), I² = 71.8%						

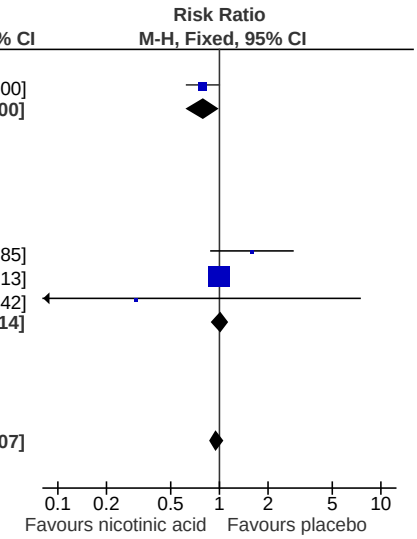


Figure 142: Hospitalisation in secondary prevention

Study or Subgroup	Nicotinic acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Nicotinic acid versus placebo						
Anon 1975 CDP	306	1073	948	2694	86.7%	0.81 [0.73, 0.90]
Subtotal (95% CI)		**1073**		**2694**	**86.7%**	**0.81 [0.73, 0.90]**
Total events	306		948			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.83 (P = 0.0001)						
1.6.2 Nicotinic acid + statin versus statin						
AIM-HIGH 2011	72	1718	82	1696	13.3%	0.87 [0.64, 1.18]
Subtotal (95% CI)		**1718**		**1696**	**13.3%**	**0.87 [0.64, 1.18]**
Total events	72		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.37)						
Total (95% CI)		**2791**		**4390**	**100.0%**	**0.82 [0.74, 0.91]**
Total events	378		1030			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						

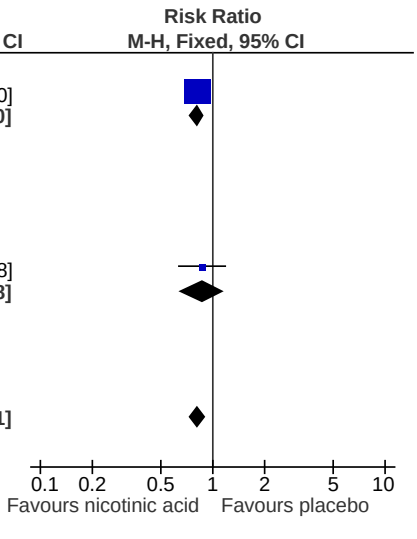


Figure 143: GI symptoms in secondary prevention

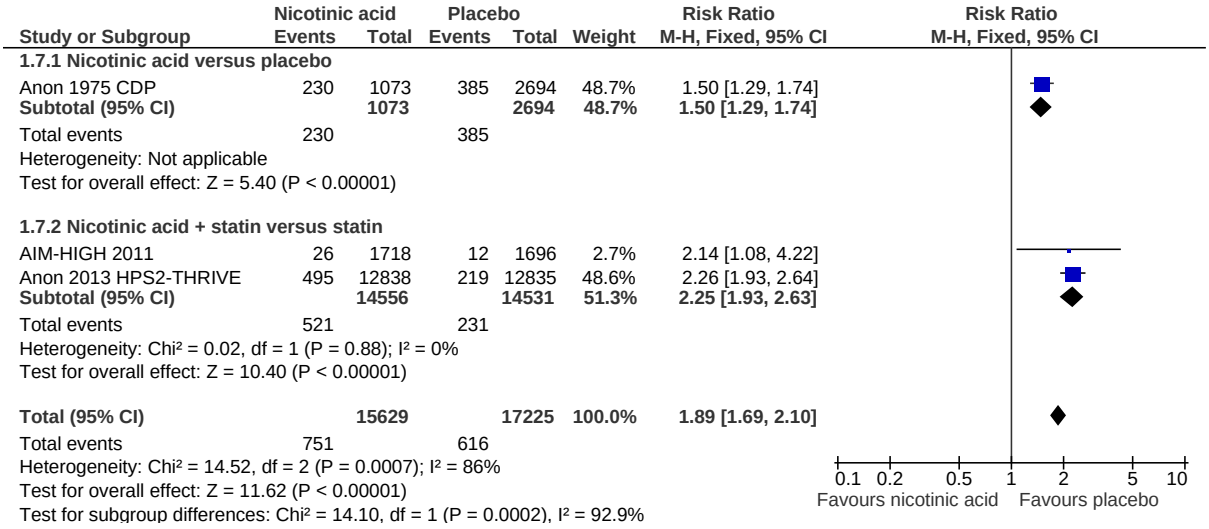


Figure 144: Flushing in secondary prevention

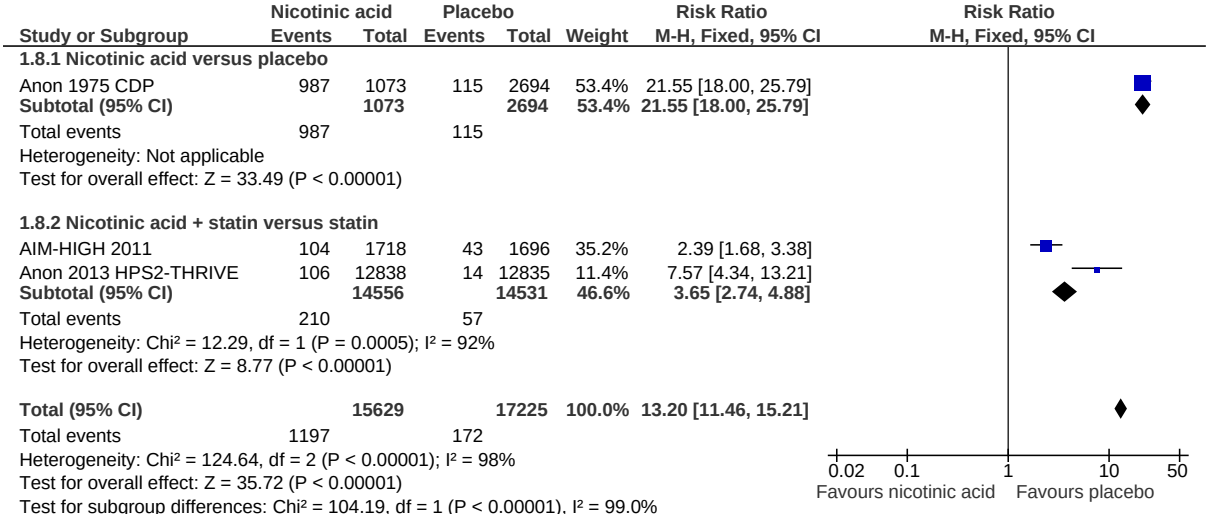


Figure 145: Itching of skin in secondary prevention

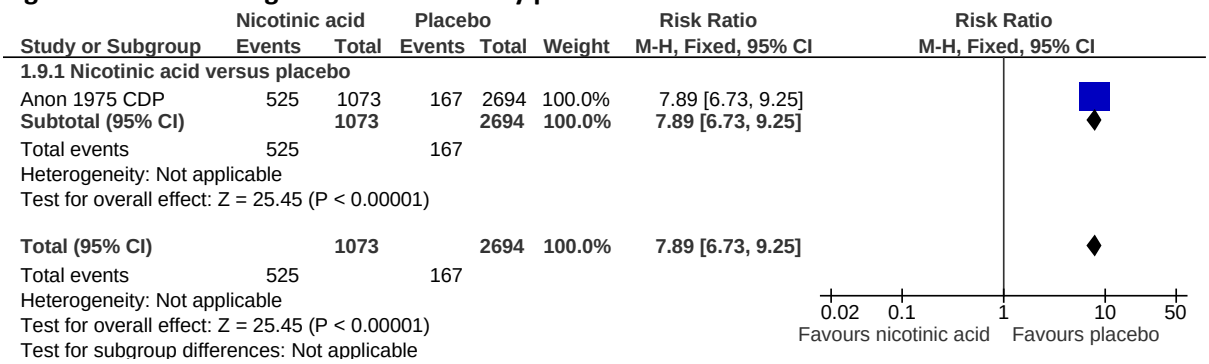


Figure 146: New onset diabetes in population subgroups; nicotinic acid versus placebo

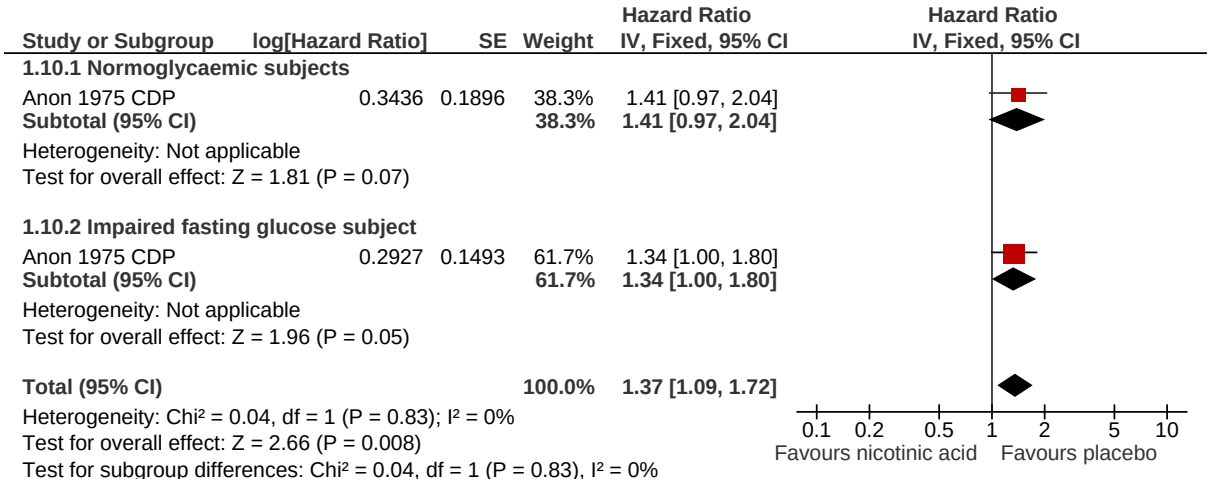


Figure 147: All-cause mortality in population subgroups; nicotinic acid versus placebo

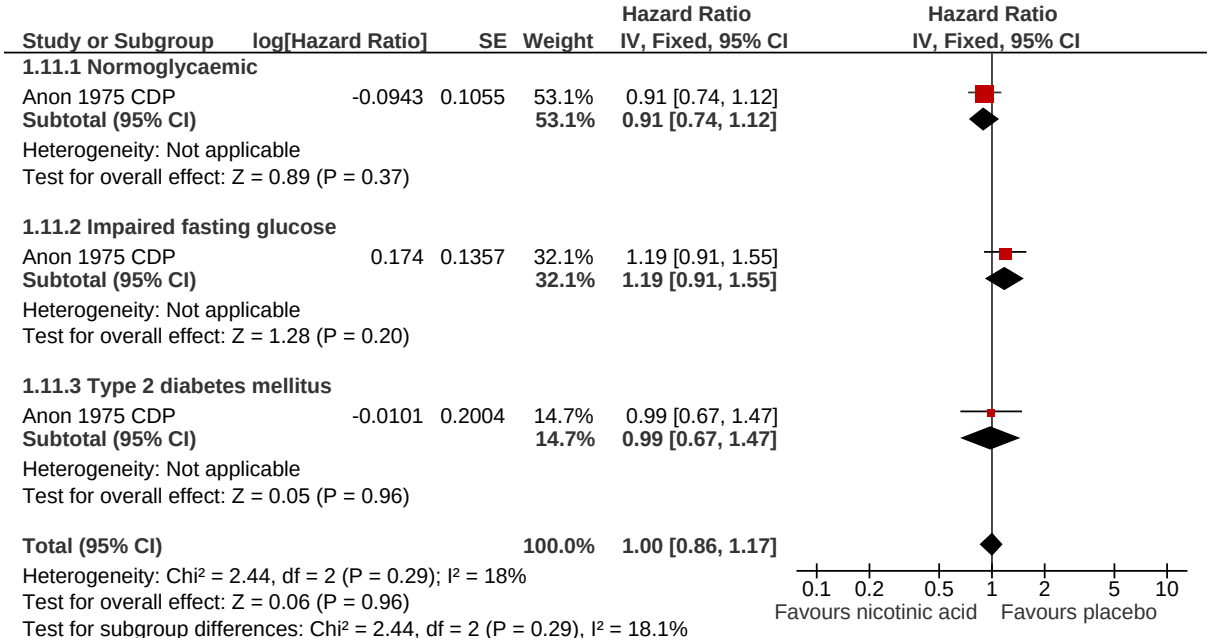


Figure 148: Non-fatal MI in population subgroups; fibrate versus placebo

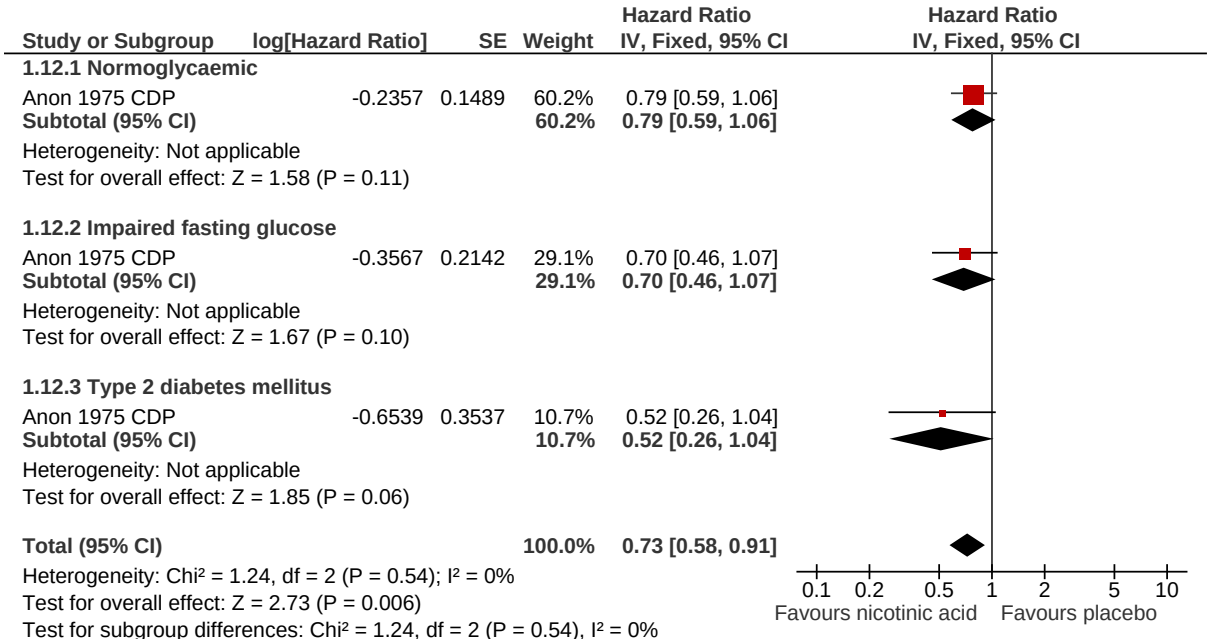


Figure 149: Abnormal liver function test in secondary prevention

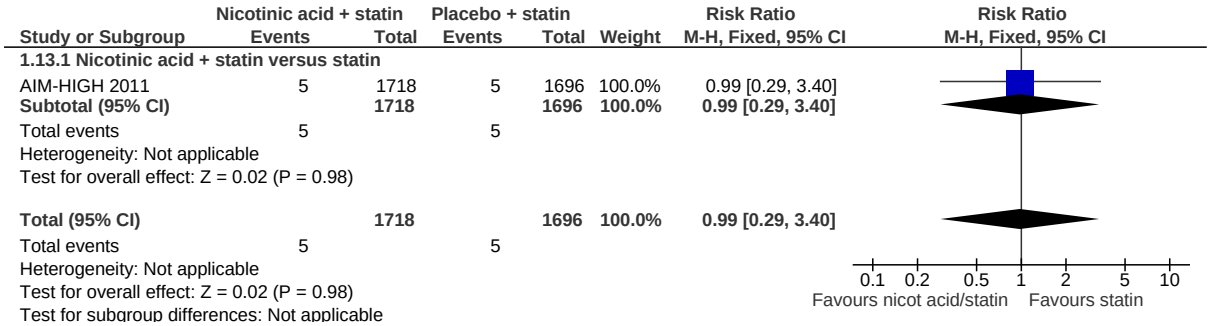


Figure 150: Increased glucose level in secondary prevention

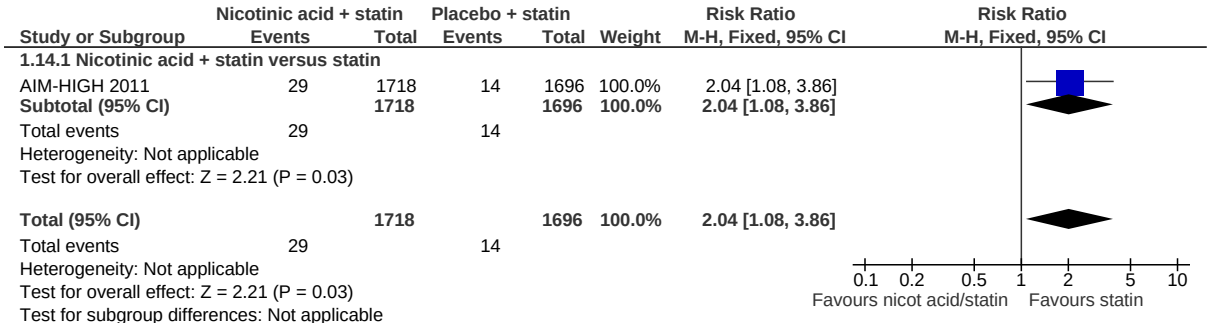


Figure 151: Alanine transaminase more than 3 times ULN in secondary prevention

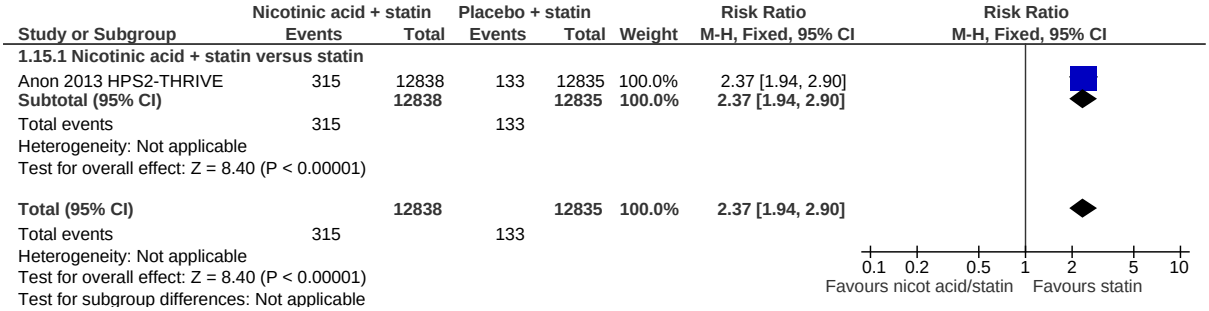


Figure 152: Rhabdomyolysis in secondary prevention

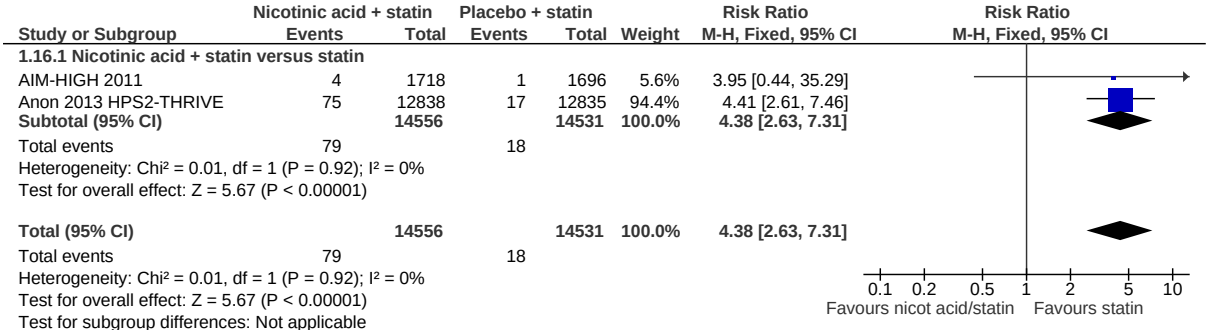
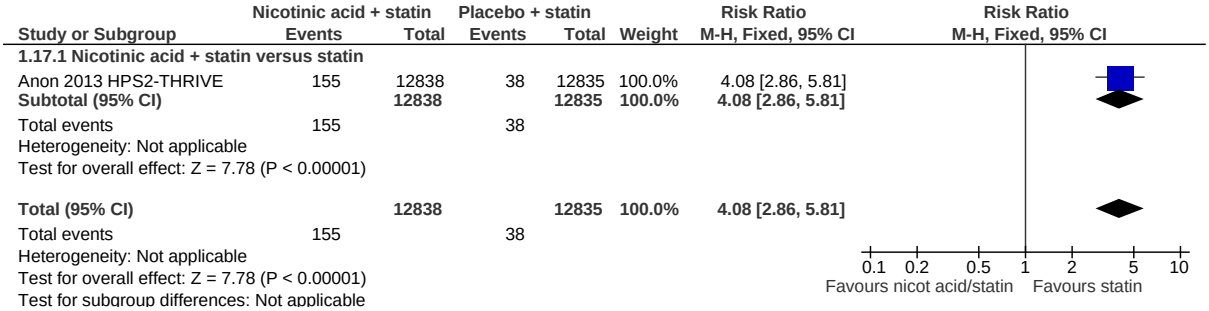


Figure 153: Myopathy in secondary prevention



I.10 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

Figure 154: All-cause mortality

Study or Subgroup	Bile acid sequestrants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Primary prevention						
LRC-CPPT 1984	68	1906	71	1900	59.5%	0.95 [0.69, 1.32]
Subtotal (95% CI)		**1906**		**1900**	**59.5%**	**0.95 [0.69, 1.32]**
Total events	68		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.1.2 Combined primary and secondary prevention (men)						
Dorr 1978 men	17	548	27	546	22.6%	0.63 [0.35, 1.14]
Subtotal (95% CI)		**548**		**546**	**22.6%**	**0.63 [0.35, 1.14]**
Total events	17		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.1.3 Combined primary and secondary prevention (women)						
Dorr 1978 women	20	601	21	583	17.8%	0.92 [0.51, 1.69]
Subtotal (95% CI)		**601**		**583**	**17.8%**	**0.92 [0.51, 1.69]**
Total events	20		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**3055**		**3029**	**100.0%**	**0.88 [0.68, 1.13]**
Total events	105		119			
Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 1.51, df = 2 (P = 0.47), I² = 0%						

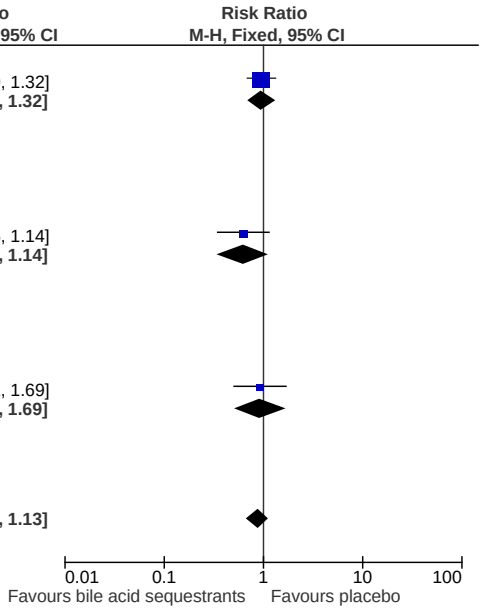


Figure 155: CV mortality

Study or Subgroup	Bile acid sequestrants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Combined primary and secondary prevention						
Dorr 1978 men	24	548	11	546	100.0%	2.17 [1.08, 4.39]
Subtotal (95% CI)		**548**		**546**	**100.0%**	**2.17 [1.08, 4.39]**
Total events	24		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						
Total (95% CI)		**548**		**546**	**100.0%**	**2.17 [1.08, 4.39]**
Total events	24		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						
Test for subgroup differences: Not applicable						

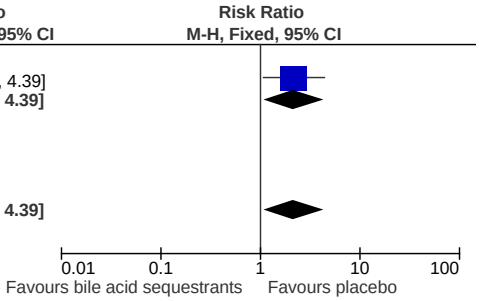


Figure 156: MI

Study or Subgroup	Bile acid sequestrants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Primary prevention						
LRC-CPPT 1984	130	1906	158	1900	99.7%	0.82 [0.66, 1.03]
Subtotal (95% CI)		**1906**		**1900**	**99.7%**	**0.82 [0.66, 1.03]**
Total events	130		158			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.3.2 Combined primary and secondary prevention						
Dorr 1978 men	8	548	0	546	0.3%	16.94 [0.98, 292.74]
Subtotal (95% CI)		**548**		**546**	**0.3%**	**16.94 [0.98, 292.74]**
Total events	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
Total (95% CI)		**2454**		**2446**	**100.0%**	**0.87 [0.70, 1.08]**
Total events	138		158			
Heterogeneity: Chi² = 4.44, df = 1 (P = 0.04); I² = 78%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Test for subgroup differences: Chi² = 4.31, df = 1 (P = 0.04), I² = 76.8%						

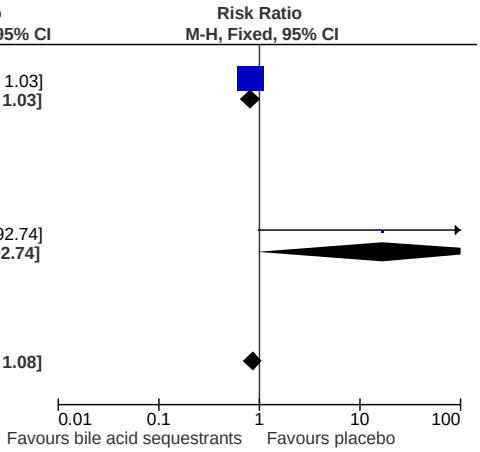


Figure 157: Sudden cardiac death

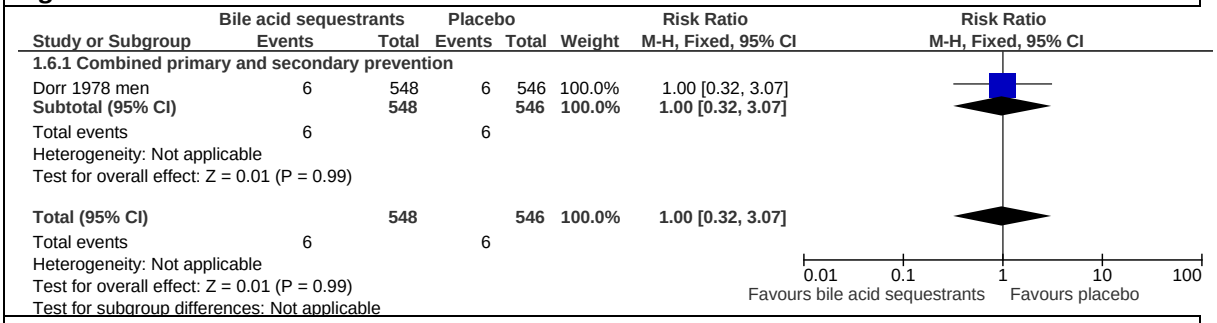


Figure 158: Hospitalisation

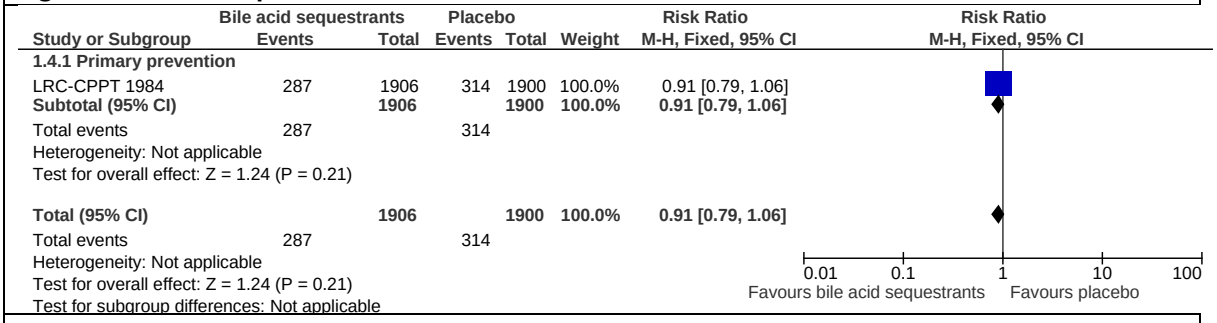
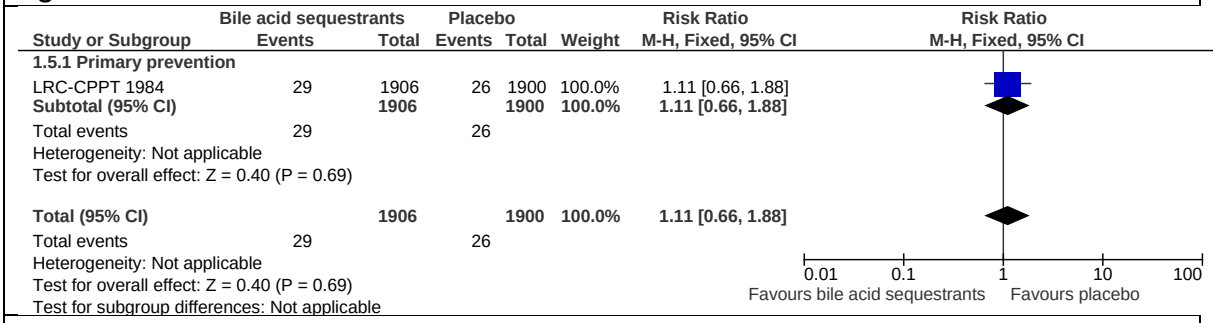
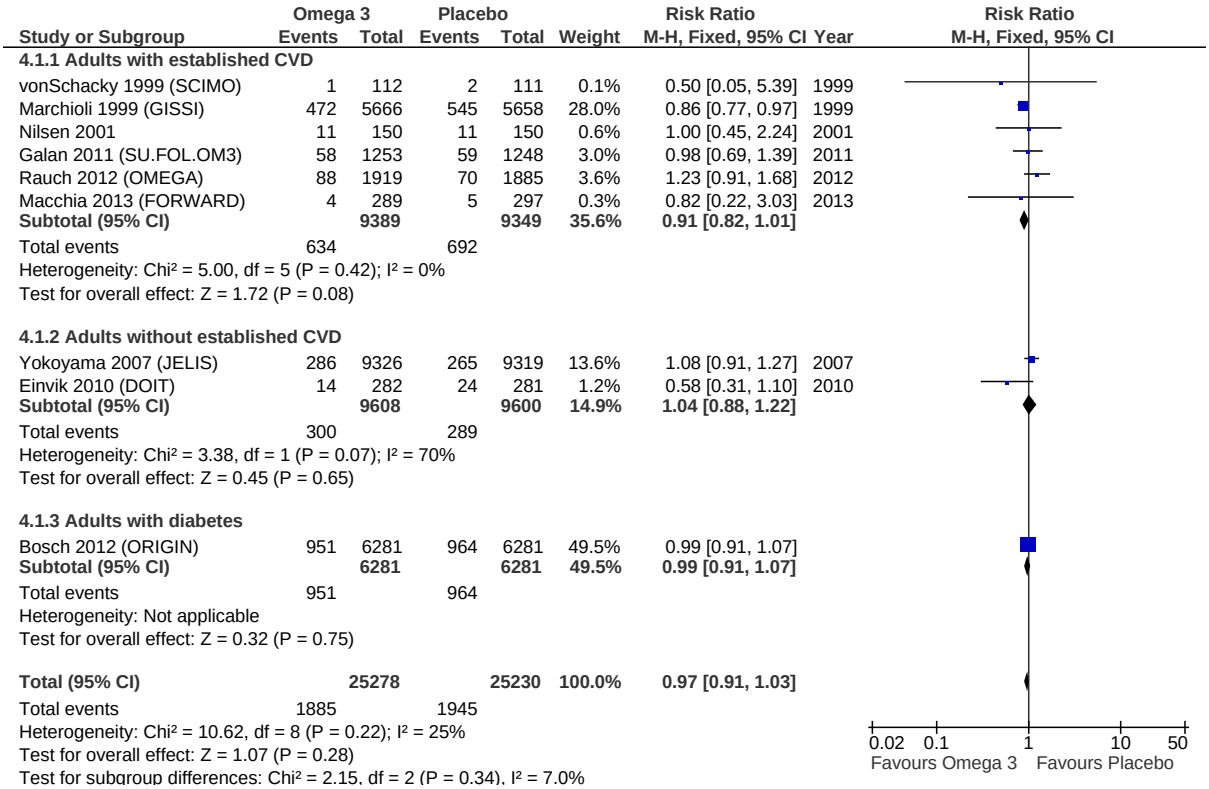


Figure 159: GI adverse events



I.11 Omega-3 fatty acid compounds for the prevention of CVD

Figure 160: All-cause mortality



JELIS trial only reported all-cause mortality for the overall population (80% primary prevention and 20% secondary prevention)

Figure 161: CV mortality

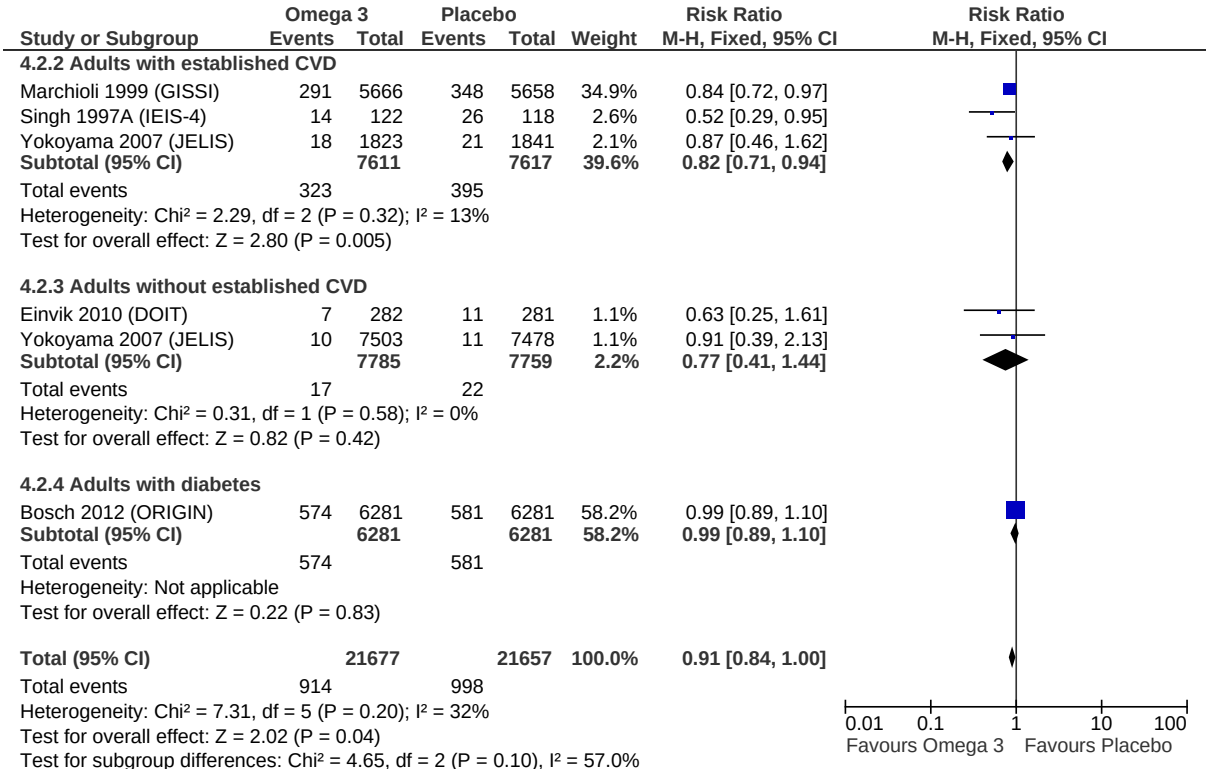


Figure 162: MI

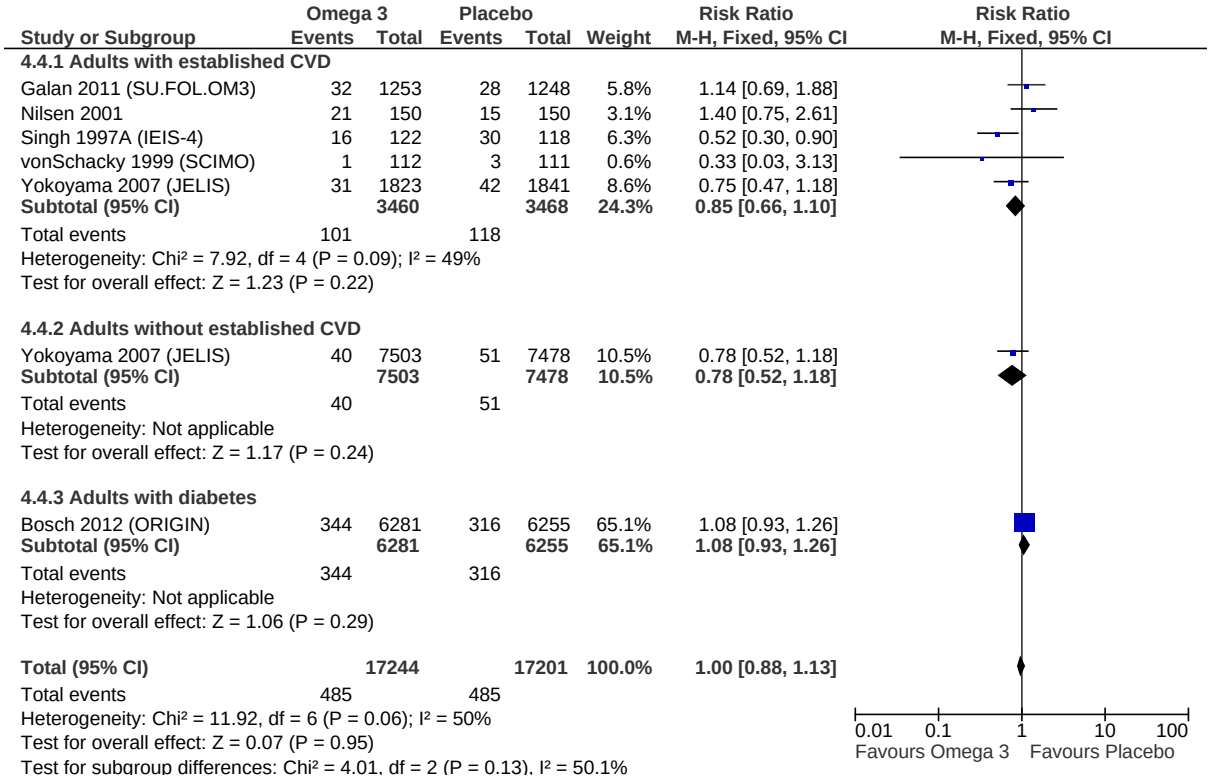
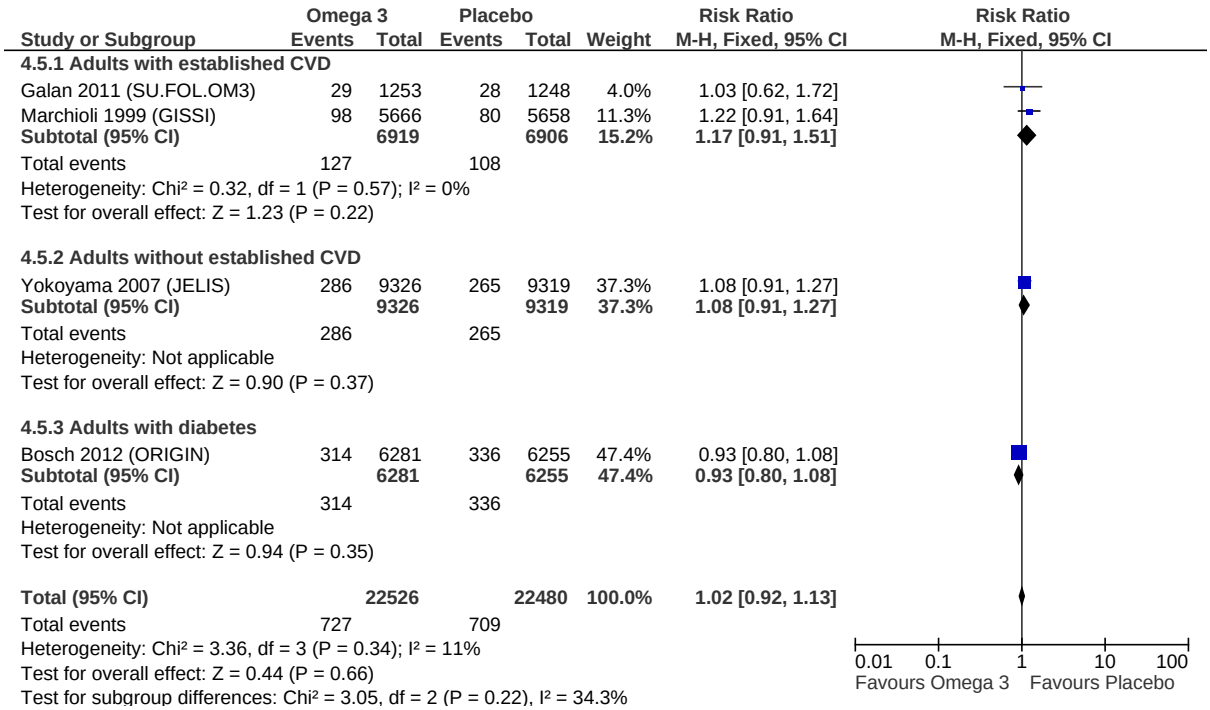
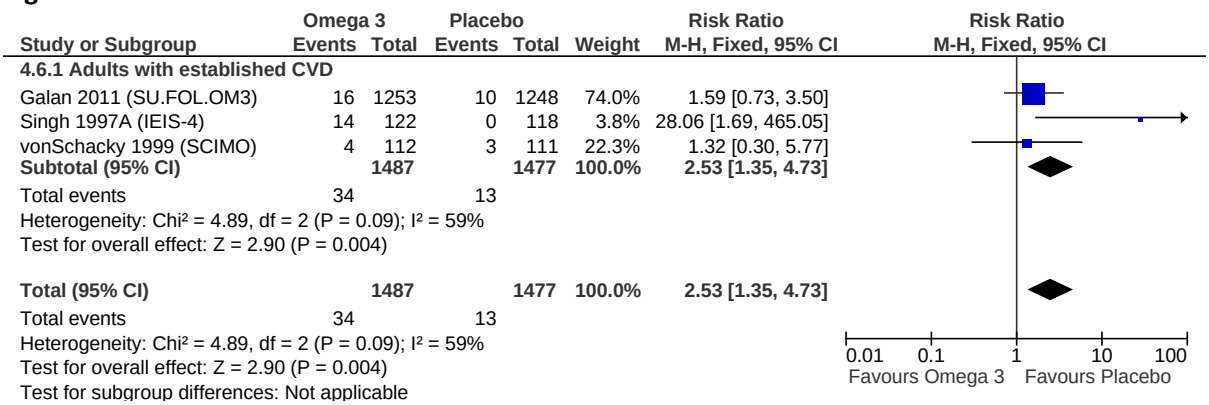


Figure 163: Stroke



JELIS trial only reported stroke for the overall population (80% primary prevention and 20% secondary prevention)

Figure 164: GI adverse events



Appendix J: Excluded clinical studies

J.1 Risk assessment tools

Reference	Reason for exclusion
Aarabi M, Jackson PR. Predicting coronary risk in UK South Asians: an adjustment method for Framingham-based tools. European Journal of Cardiovascular Prevention and Rehabilitation. 2005; 12(1):46-51. (Guideline Ref ID AARABI2005 [49])	Wrong study design (cross-sectional)
Adler AI. UKPDS-modelling of cardiovascular risk assessment and lifetime simulation of outcomes. Diabetic Medicine. 2008; 25 Suppl 2:41-46. (Guideline Ref ID ADLER2008 [61])	Narrative review
Ahn HR, Shin MH, Yun WJ, Kim HY, Lee YH, Kweon SS et al. Comparison of the Framingham Risk Score, UKPDS Risk Engine, and SCORE for Predicting Carotid Atherosclerosis and Peripheral Arterial Disease in Korean Type 2 Diabetic Patients. Korean Journal of Family Medicine. 2011; 32(3):189-196. (Guideline Ref ID AHN2011 [67])	Wrong population (not from England or Wales)
Almeda-Valdes P, Cuevas-Ramos D, Mehta R, Gomez-Perez FJ, Aguilar-Salinas CA. UKPDS Risk Engine, DECODE and diabetes PHD models for the estimation of cardiovascular risk in patients with diabetes. Current Diabetes Reviews. 2010; 6(1):1-8. (Guideline Ref ID ALMEDAVALDES2010 [77])	Wrong population (not from England or Wales)
Ankle B, I, Fowkes FGR, Murray GD, Butcher I, Heald CL, Lee RJ et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008; 300(2):197-208. (Guideline Ref ID ANKLE2008 [96])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Arsenault BJ, Rana JS, Lemieux I, Despres JP, Wareham NJ, Kastelein JJP et al. Physical activity, the Framingham risk score and risk of coronary heart disease in men and women of the EPIC-Norfolk study. Atherosclerosis. 2010; 209(1):261-265. (Guideline Ref ID ARSENAULT2010 [111])	No outcomes of interest
Barreto SM, Passos VMA, Cardoso ARA, Lima-Costa MF. Quantifying the risk of coronary artery disease in a community: the Bambui project. Arquivos Brasileiros De Cardiologia. 2003; 81(6):556-55. (Guideline Ref ID BARRETO2003 [142])	Wrong population (not from England or Wales)
Barroso LC, Muro EC, Herrera ND, Ochoa GF, Hueros JIC, Buitrago F. Performance of the Framingham and SCORE cardiovascular risk prediction functions in a non-diabetic population of a Spanish health care centre: a validation study. Scandinavian Journal of Primary Health Care. 2010; 28(4):242-248. (Guideline Ref ID BARROSO2010 [144])	Wrong population (not from England or Wales)
Bastuji-Garin S, Deverly A, Moyse D, Castaigne A, Mancia G, de Leeuw PW et al. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. Journal of Hypertension. 2002; 20(10):1973-1980. (Guideline Ref ID BASTUJIGARIN2002 [148])	Wrong population (not from England or Wales)
Baxi NS, Jackson JL, Ritter J, Sessums LL. How well do the Framingham risk factors correlate with diagnoses of ischemic heart disease and cerebrovascular disease in a military beneficiary cohort? Military Medicine. 2011; 176(4):408-413. (Guideline Ref ID BAXI2011 [150])	No outcomes of interest
Beer C, Alfonso H, Flicker L, Norman PE, Hankey GJ, Almeida OP. Traditional risk factors for incident cardiovascular events have limited importance in later life compared with the health in men study cardiovascular risk score. Stroke; a Journal of Cerebral Circulation. 2011; 42(4):952-959. (Guideline Ref ID BEER2011 [153])	Wrong population (not from England or Wales)
Benchimol D, Pillois X, Oysel-Mestre M, Sagardiluz P, Bonnet J. Ankle brachial index using an automatic blood pressure device in occupational medicine: relevance in routine examination and comparison with Framingham cardio-	No outcomes of interest

Reference	Reason for exclusion
vascular risk score. International Journal of Clinical Practice. 2012; 66(9):862-866. (Guideline Ref ID BENCHIMOL2012 [162])	
Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for Cardiovascular Risk in Asymptomatic Patients. Journal of the American College of Cardiology. 2010; 55(12):1169-1177. (Guideline Ref ID BERGER2010 [167])	Systematic review with different inclusion criteria from review protocol
Berry JD, Lloyd-Jones DM, Garside DB, Greenland P. Framingham risk score and prediction of coronary heart disease death in young men. American Heart Journal. 2007; 154(1):80-86. (Guideline Ref ID BERRY2007 [169])	Wrong population (not from England or Wales)
Bertrand M, Eid S, Moran L, Xiang Y, Fugate T, Matsumura ME. Famingham risk score inadequately identifies patients at risk of a first ST elevation myocardial infarction. Internet Journal of Cardiology. 2009; 7(2). (Guideline Ref ID BERTRAND2009 [171])	No outcomes of interest
Bineau S, Dufouil C, Helmer C, Ritchie K, Empana JP, Ducimetiere P et al. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. Stroke; a Journal of Cerebral Circulation. 2009; 40(5):1564-1570. (Guideline Ref ID BINEAU2009 [182])	Wrong population (not from England or Wales)
Block R, Kakinami L, Liebman S, Shearer GC, Kramer H, Tsai M. Cis-vaccenic acid and the Framingham risk score predict chronic kidney disease: the multi-ethnic study of atherosclerosis (MESA). Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2012; 86(4-5):175-182. (Guideline Ref ID BLOCK2012 [189])	No outcomes of interest
Brekke M, Straand J. Does present use of cardiovascular medication reflect elevated cardiovascular risk scores estimated ten years ago? A population based longitudinal observational study. BMC Public Health. 2011; 11:144. (Guideline Ref ID BREKKE2011 [212])	Wrong population (not from England or Wales)
Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart. 2006; 92(12):1752-1759. (Guideline Ref ID BRINDLE2006 [218])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Brindle P, May M, Gill P, Cappuccio F, D'Agostino RS, Fischbacher C et al. Primary prevention of cardiovascular disease: a web-based risk score for seven British black and minority ethnic groups. Heart. 2006; 92(11):1595-1602. (Guideline Ref ID BRINDLE2006A [219])	No outcomes of interest
Brindle PM, McConnachie A, Upton MN, Hart CL, Davey Smith G, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. British Journal of General Practice. 2005; 55(520):838-845. (Guideline Ref ID BRINDLE2005 [221])	Wrong population (not from England or Wales)
Brouwers FP, de Boer RA, van der Harst P, Struck J, de Jong PE, de Zeeuw D et al. Influence of age on the prognostic value of mid-regional pro-adrenomedullin in the general population. Heart. 2012; 98(18):1348-1353. (Guideline Ref ID BROUWERS2012 [226])	Wrong population (not from England or Wales)
Buitrago F, Calvo-Hueros JI, Canon-Barroso L, Pozuelos-Estrada G, Molina-Martinez L, Espigares-Arroyo M et al. Original and REGICOR Framingham functions in a nondiabetic population of a Spanish health care center: a validation study. Annals of Family Medicine. 2011; 9(5):431-438. (Guideline Ref ID BUITRAGO2011 [246])	Wrong population (not from England or Wales)
Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia. 2009; 52(10):2001-2014. (Guideline Ref ID CHAMNAN2009 [288])	Systematic review with different inclusion criteria (includes non UK studies). Single relevant studies included.
Chan SY, Kaneshanathan A, McCormick C, Webb H, Pakianathan M, Hay P.	Conference abstract

Reference	Reason for exclusion
Comparison of Qrisk 2 and DAD cardiovascular risk scores in HIV positive patients with an identified ten year Framingham risk of >=10%. HIV Medicine. 2012; 13:80. (Guideline Ref ID CHAN2012 [295])	
Chang A, Kramer H. Should eGFR and albuminuria be added to the Framingham risk score? Chronic kidney disease and cardiovascular disease risk prediction. Nephron Clinical Practice. 2011; 119(2):c171-c178. (Guideline Ref ID CHANG2011A [296])	Wrong population (not from England or Wales)
Christianson TJH, Bryant SC, Weymiller AJ, Smith SA, Montori VM. A pen-and-paper coronary risk estimator for office use with patients with type 2 diabetes. Mayo Clinic Proceedings. 2006; 81(5):632-638. (Guideline Ref ID CHRISTIANSON2006A [319])	Wrong population (not from England or Wales)
Colkesen BE, Jorstad HT, Boekholdt SM, Wareham NJ, Tijssen JGP, Peters RJG et al. Performance of the SCORE risk function in predicting 10-year cardiovascular mortality: Predicted versus observed mortality in a large population-based cohort. European Heart Journal. 2010; 31:939. (Guideline Ref ID COLKESEN2010 [334])	Conference abstract
Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: A prospective open cohort study. BMJ. 2009; 339(7713):144-147. (Guideline Ref ID COLLINS2009A [336])	Wrong index test (QRISK. A more up to date version has been included, QRISK2)
Conde DM, De Sousa EP, Costa-Paiva LS, Martinez EZ, Pinto-Neto AM. Risk of cardiovascular disease in middle-aged breast cancer survivors assessed by the Framingham and SCORE models. Menopause. 2012; 19(12):1394-1395. (Guideline Ref ID CONDE2012 [342])	Conference abstract
Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal. 2003; 24(11):987-1003. (Guideline Ref ID CONROY2003 [345])	Wrong index test (SCORE)
Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG et al. Circulation. 2012; 125(14):1748-1756. (Guideline Ref ID COOK2012A [348])	Wrong population (not from England or Wales)
Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG et al. Validation of framingham and reynolds cardiovascular risk prediction models in the women's health initiative. Circulation. 2011; 124(21 SUPPL. 1). (Guideline Ref ID COOK2011 [347])	Conference abstract
Cooney MT, Selmer R, Lindman A, Dudina A, Tverdal A, Graham IM. SCORE OP: Derivation and validation of a function for estimating CVD risk in older people. European Heart Journal. 2011; 32:544. (Guideline Ref ID COONEY2011A [349])	Conference abstract
Cortes-Bergoderi M, Thomas RJ, Albuquerque FN, Batsis JA, Burdiat G, Perez-Terzic C et al. Validity of cardiovascular risk prediction models in Latin America and among Hispanics in the United States of America: a systematic review. Revista Panamericana De Salud Publica. 2012; 32(2):131-139. (Guideline Ref ID CORTESBERGODERI2012 [353])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
D'Agostino RBS, Grundy S, Sullivan LM, Wilson P, CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001; 286(2):180-187. (Guideline Ref ID DAGOSTINO2001 [373])	Wrong population (not from England or Wales)
D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omede P, Sciuto F et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemporary Clinical Trials. 2012; 33(3):507-514. (Guideline Ref ID DASCENZO2012 [374])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Damkondwar DR, Raman R, Suganeswari G, Kulothungan V, Sharma T. Assessing Framingham cardiovascular risk scores in subjects with diabetes and their	Wrong population (not from England or

Reference	Reason for exclusion
correlation with diabetic retinopathy. Indian Journal of Ophthalmology. 2012; 60(1):45-48. (Guideline Ref ID DAMKONDWAR2012 [378])	Wales)
Davis TME, Coleman RL, Holman RR, UKPDS Group. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation. 2013; 127(9):980-987. (Guideline Ref ID DAVIS2013 [387])	No outcomes of interest
Davis WA, Colagiuri S, Davis TME. Comparison of the Framingham and United Kingdom Prospective Diabetes Study cardiovascular risk equations in Australian patients with type 2 diabetes from the Fremantle Diabetes Study. Medical Journal of Australia. 2009; 190(4):180-184. (Guideline Ref ID DAVIS2009 [388])	Wrong population (not from England or Wales)
De Bacquer D, De Backer G. Predictive ability of the SCORE Belgium risk chart for cardiovascular mortality. International Journal of Cardiology. 2010; 143(3):385-390. (Guideline Ref ID DEBACQUER2010 [391])	Wrong index test (SCORE)
de la Iglesia B, Potter JF, Poulter NR, Robins MM, Skinner J. Performance of the ASSIGN cardiovascular disease risk score on a UK cohort of patients from general practice. Heart. 2011; 97(6):491-499. (Guideline Ref ID DELAIGLESIA2011 [396])	Wrong index test (ASSIGN)
de Padua Netto MV, Bonfim TCC, Costa EN, de Lima HV, Netto LCP. Cardiovascular risk estimated in renal transplant recipients with the Framingham score. Transplantation Proceedings. 2012; 44(8):2337-2340. (Guideline Ref ID DEPADUANETTO2012 [409])	No outcomes of interest
de Ruijter W, Westendorp RGJ, Assendelft WJJ, den Elzen WPJ, de Craen AJM, le Cessie S et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ. 2009; 338:a3083. (Guideline Ref ID DERUIJTER2009 [410])	Wrong population (not from England or Wales)
DeGoma EM, Dunbar RL, Jacoby D, French B. Differences in absolute risk of cardiovascular events using risk-refinement tests: A systematic analysis of four cardiovascular risk equations. Atherosclerosis. 2013; 227(1):172-177. (Guideline Ref ID DEGOMA2013 [413])	Meta-analysis; inclusion criteria different from review protocol (includes MESA, ARIC and Reynolds)
Drawz PE, Baraniuk S, Davis BR, Brown CD, Colon PJS, Cujyet AB et al. Cardiovascular risk assessment: addition of CKD and race to the Framingham equation. American Heart Journal. 2012; 164(6):925-931. (Guideline Ref ID DRAWZ2012 [445])	Wrong population (not from England or Wales)
Eichler K, Puhan MA, Steurer J, Bachmann LM. Prediction of first coronary events with the Framingham score: a systematic review. American Heart Journal. 2007; 153(5):722-728. (Guideline Ref ID EICHLER2007 [455])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Ezenwaka CE, Nwagbara E, Seales D, Okali F, Hussaini S, Raja B et al. Prediction of 10-year coronary heart disease risk in Caribbean type 2 diabetic patients using the UKPDS risk engine. International Journal of Cardiology. 2009; 132(3):348-353. (Guideline Ref ID EZENWAKA2009 [484])	Wrong population (not from England or Wales)
Feinleib M, Kannel WB, Garrison RJ. The Framingham offspring study. Design and preliminary data. Preventive Medicine. 1975; 4(4):518-525. (Guideline Ref ID FEINLEIB1975 [495])	No outcomes of interest
Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. American Heart Journal. 2009; 157(6):988-994. (Guideline Ref ID FISCELLA2009 [501])	Wrong population (not from England or Wales)
Game FL, Bartlett WA, Bayly GR, Jones AF. Comparative accuracy of cardiovascular risk prediction methods in patients with diabetes mellitus. Diabetes, Obesity and Metabolism. 2001; 3(4):279-286. (Guideline Ref ID GAME2001 [535])	Wrong study design (database, no follow up)

Reference	Reason for exclusion
Game FL, Jones AF. Coronary heart disease risk assessment in diabetes mellitus--a comparison of PROCAM and Framingham risk assessment functions. Diabetic Medicine. 2001; 18(5):355-359. (Guideline Ref ID GAME2001A [536])	No outcomes of interest
Guckelberger O, Mutzke F, Glanemann M, Neumann UP, Jonas S, Neuhaus R et al. Validation of cardiovascular risk scores in a liver transplant population. Liver Transplantation. 2006; 12(3):394-401. (Guideline Ref ID GUCKELBERGER2006 [592])	Wrong population (not from England or Wales)
Halcox JPJ, Tubach F, Banegas JR, Borghi C, Dallongeville J, De BG et al. Reclassification of cardiovascular risk in Europe: Application of the updated Systematic COronary Risk Evaluation (SCORE) algorithm incorporating high-density lipoprotein levels. European Heart Journal. 2012; 33:1060. (Guideline Ref ID HALCOX2012 [608])	Conference abstract
Haq IU, Ramsay LE, Jackson PR, Wallis EJ. Prediction of coronary risk for primary prevention of coronary heart disease: a comparison of methods. Qjm. 1999; 92(7):379-385. (Guideline Ref ID HAQ1999 [617])	Wrong index tests (European Task Force chart and Sheffield table)
Hari PK, Antoun P, Vanthof J, Foster GP. Predictive value of framingham risk and coronary calcium in high and low risk populations. Circulation. 2012; 126(21 SUPPL. 1). (Guideline Ref ID HARI2012A [618])	Conference abstract
Hemann BA, Bimson WF, Taylor AJ. The Framingham Risk Score: an appraisal of its benefits and limitations. American Heart Hospital Journal. 2007; 5(2):91-96. (Guideline Ref ID HEMANN2007 [637])	No outcomes of interest
Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany--results from the MONICA Augsburg and the PROCAM cohorts. European Heart Journal. 2003; 24(10):937-945. (Guideline Ref ID HENSE2003 [638])	Wrong population (not from England or Wales)
Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Brindle P. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. Heart. 2008; 94(1):34-39. (Guideline Ref ID HIPPISLEYCOX2008A [647])	Wrong index test (QRISK. A more up to date version has been included, QRISK2)
Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007; 335(7611):136. (Guideline Ref ID HIPPISLEYCOX2007 [651])	Wrong index test (QRISK. A more up to date version has been included, QRISK2)
Hippisley-Cox,Julia; Coupland,Carol; Brindle,Peter. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. BMJ 2013; 346: f2573 (Guideline Ref ID HIPPISLEYCOX2013 [649])	Wrong index test (QStroke has not been externally validated in the UK)
Hurley LP, Dickinson LM, Estacio RO, Steiner JF, Havranek EP. Prediction of cardiovascular death in racial/ethnic minorities using Framingham risk factors. Circulation Cardiovascular Quality and Outcomes. 2010; 3(2):181-187. (Guideline Ref ID HURLEY2010 [687])	Wrong population (not from England or Wales)
Hurst RT, Nelson MR, Eleid M, Nelson KG, Lester SJ. Individualized cardiac risk assessment: Subclinical atherosclerosis and the 30 year Framingham risk score. European Heart Journal. 2011; 32:223. (Guideline Ref ID HURST2011 [688])	Conference abstract
Jovicic S, Ignjatovic S, Majkic-Singh N. Comparison of two different methods for cardiovascular risk assessment: Framingham risk score and SCORE system. Journal of Medical Biochemistry. 2007; 26(2):94-97. (Guideline Ref ID JOVICIC2007 [725])	Wrong population (not from England or Wales)
Kaffashian S, Dugravot A, Elbaz A, Shipley MJ, Sabia S, Kivimaki M et al. Predicting cognitive decline: A dementia risk score vs the Framingham vascular risk scores. Neurology. 2013; 80(14):1300-1306. (Guideline Ref ID KAFFASHIAN2013 [730])	Wrong population (not from England or Wales)
Kengne AP, Patel A, Colagiuri S, Heller S, Hamet P, Marre M et al. The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate	Wrong population (not from England or

Reference	Reason for exclusion
the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study. Diabetologia. 2010; 53(5):821-831. (Guideline Ref ID KENGNE2010 [749])	Wales)
Khalili D, Hadaegh F, Soori H, Steyerberg EW, Bozorgmanesh M, Azizi F. Clinical usefulness of the Framingham cardiovascular risk profile beyond its statistical performance: the Tehran Lipid and Glucose Study. American Journal of Epidemiology. 2012; 176(3):177-186. (Guideline Ref ID KHALILI2012 [751])	Wrong population (not from England or Wales)
Khan Z, Almeida DRP, Rahim K, Belliveau MJ, Bona M, Gale J. 10-Year Framingham risk in patients with retinal vein occlusion: a systematic review and meta-analysis. Canadian Journal of Ophthalmology Journal Canadien D'Ophtalmologie. 2013; 48(1):40-45. (Guideline Ref ID KHAN2013 [752])	No outcomes of interest
Kiberd B, Panek R. Cardiovascular outcomes in the outpatient kidney transplant clinic: the Framingham risk score revisited. Clinical Journal of the American Society of Nephrology. 2008; 3(3):822-828. (Guideline Ref ID KIBERD2008 [758])	Wrong population (not from England or Wales)
Kirk JK, Bertoni AG, Case D, Bell RA, Goff DCJ, Narayan KMV. Predicted risk of coronary heart disease among persons with type 2 diabetes. Coronary Artery Disease. 2007; 18(8):595-600. (Guideline Ref ID KIRK2007 [763])	Wrong population (not from England or Wales)
Knobel H, Jerico C, Montero M, Sorli ML, Velat M, Guelar A et al. Global cardiovascular risk in patients with HIV infection: concordance and differences in estimates according to three risk equations (Framingham, SCORE, and PROCAM). AIDS Patient Care and STDs. 2007; 21(7):452-457. (Guideline Ref ID KNOBEL2007 [770])	Wrong population (not from England or Wales)
Koller MT, Leening MJG, Wolbers M, Steyerberg EW, Hunink MGM, Schoop R et al. Development and validation of a coronary risk prediction model for older U.S. and European persons in the cardiovascular health study and the Rotterdam Study. Annals of Internal Medicine. 2012; 157(6):389-397. (Guideline Ref ID KOLLER2012 [775])	Wrong population (not from England or Wales)
Koller MT, Steyerberg EW, Wolbers M, Stijnen T, Bucher HC, Hunink MGM et al. Validity of the Framingham point scores in the elderly: results from the Rotterdam study. American Heart Journal. 2007; 154(1):87-93. (Guideline Ref ID KOLLER2007 [776])	Wrong population (not from England or Wales)
Lambert AP, Hunt MA, Day AP, Bayly GR, Dayan CM. Reproducibility of individualized coronary heart disease risk calculations in patients with diabetes mellitus. Diabetic Medicine. 2002; 19(6):514-517. (Guideline Ref ID LAMBERT2002 [808])	No outcomes of interest
Lau KK, Chan YH, Yiu KH, Tam S, Li SW, Lau CP et al. Incremental predictive value of vascular assessments combined with the Framingham Risk Score for prediction of coronary events in subjects of low-intermediate risk. Postgraduate Medical Journal. 2008; 84(989):153-157. (Guideline Ref ID LAU2008 [814])	Wrong study design (case–control)
Leaverton PE, Sorlie PD, Kleinman JC, Dannenberg AL, Ingster-Moore L, Kannel WB et al. Representativeness of the Framingham risk model for coronary heart disease mortality: a comparison with a national cohort study. Journal of Chronic Diseases. 1987; 40(8):775-784. (Guideline Ref ID LEAVERTON1987 [822])	No outcomes of interest
Lee GKM, Lee LC, Liu CWY, Lim SL, Shi LM, Ong HY et al. Framingham risk score inadequately predicts cardiac risk in young patients presenting with a first myocardial infarction. Annals of the Academy of Medicine, Singapore. 2010; 39(3):163-167. (Guideline Ref ID LEE2010 [823])	Wrong population (not from England or Wales)
Lengele JP, Vinck WJ, De Plaen JF, Persu A. Cardiovascular risk assessment in hypertensive patients: major discrepancy according to ESH and SCORE strategies. Journal of Hypertension. 2007; 25(4):757-762. (Guideline Ref ID LENGELE2007 [831])	Wrong index test (SCORE)
Liao Y, McGee DL, Cooper RS, Sutkowski MB. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts.	Wrong population (not from England or

Reference	Reason for exclusion
American Heart Journal. 1999; 137(5):837-845. (Guideline Ref ID LIAO1999 [845])	Wales)
Liew SM, Doust J, Glasziou P. Cardiovascular risk scores do not account for the effect of treatment: a review. Heart. 2011; 97(9):689-697. (Guideline Ref ID LIEW2011 [847])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Lin CY, Lina JW. Association of framingham risk score with chronic kidney disease - Insight from national health and nutrition examination survey 2003-2006. Kidney Research and Clinical Practice. 2012; 31(2):A52. (Guideline Ref ID LIN2012 [849])	Conference abstract
Lin J-W, Lin L-Y, Lin C-Y, Kuo H-K. Association of Framingham risk score with chronic kidney disease: Insight from national health and nutrition examination survey 2003-2006. Journal of the American College of Cardiology. 2009; 53(10):A222. (Guideline Ref ID LIN2009 [850])	Conference abstract
Lloyd-Jones DM, Wilson PWF, Larson MG, Beiser A, Leip EP, D'Agostino RB et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. American Journal of Cardiology. 2004; 94(1):20-24. (Guideline Ref ID LLOYDJONES2004 [858])	Wrong population (not from England or Wales)
Lluis-Ganella C, Subirana I, Lucas G, Tomas M, Munoz D, Senti M et al. Assessment of the value of a genetic risk score in improving the estimation of coronary risk. Atherosclerosis. 2012; 222(2):456-463. (Guideline Ref ID LLUIS2012 [859])	Wrong population (not from England or Wales)
Lutgers HL, Gerrits EG, Graaff R, Links TP, Sluiter WJ, Gans RO et al. Skin autofluorescence provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in type 2 diabetes mellitus. Diabetologia. 2009; 52(5):789-797. (Guideline Ref ID LUTGERS2009 [869])	Wrong population (not from England or Wales)
Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA et al. Usefulness of the Framingham risk score and body mass index to predict early coronary artery calcium in young adults (Muscatine Study). American Journal of Cardiology. 2001; 88(5):509-515. (Guideline Ref ID MAHONEY2001 [886])	Wrong population (not from England or Wales)
Manavi K, McDermott R, Cramb R. Comparison of modified Framingham and QRISK2-2011 cardiovascular risk assessment tools in a HIV-1 infected cohort. HIV Medicine. 2012; 13:50-51. (Guideline Ref ID MANAVI2012 [890])	Conference abstract
Mannan H, Stevenson C, Peeters A, Walls H, McNeil J. Framingham risk prediction equations for incidence of cardiovascular disease using detailed measures for smoking. Heart International. 2010; 5(2):e11. (Guideline Ref ID MANNAN2010 [894])	Wrong population (not from England or Wales)
Mansell H, Worobetz LJ, Sylwestrowicz T, Shoker AS. A retrospective study of the Framingham cardiovascular risk scores in a liver transplant population. Transplantation Proceedings. 2013; 45(1):308-314. (Guideline Ref ID MANSELL2013 [901])	Wrong population (post-liver transplant)
Mcgorrian CM, Fitzgerald AP, Cooney MT, Dudina A, Whincup P, Vartiainen E et al. Estimation of ten-year risk of combined fatal and non fatal cardiovascular events: the SCOREplus study. European Heart Journal. 2010; 31:805. (Guideline Ref ID MCGORRIAN2010 [944])	Conference abstract
Mehta RL, Davies MJ, Baker R, Blackledge H, Gray LJ, Stone M et al. The accuracy of the modified Framingham and United Kingdom prospective diabetes study cardiovascular risk algorithms in a multi-ethnic population with type 2 diabetes: A longitudinal study in 4463 people over 5 years. Diabetic Medicine. 2010; 27(2 SUPPL. 1):18-19. (Guideline Ref ID MEHTA2010 [953])	Conference abstract
Milne R, Gamble G, Whitlock G, Jackson R. Discriminative ability of a risk-prediction tool derived from the Framingham Heart Study compared with single risk factors. New Zealand Medical Journal. 2003; 116(1185):U663. (Guideline Ref ID MILNE2003 [962])	Wrong population (not from England or Wales)

Reference	Reason for exclusion
Milne R, Gamble G, Whitlock G, Jackson R. Framingham Heart Study risk equation predicts first cardiovascular event rates in New Zealanders at the population level. New Zealand Medical Journal. 2003; 116(1185):U662. (Guideline Ref ID MILNE2003A [963])	Wrong population (not from England or Wales)
Mora S, Redberg RF, Sharrett AR, Blumenthal RS. Enhanced risk assessment in asymptomatic individuals with exercise testing and Framingham risk scores. Circulation. 2005; 112(11):1566-1572. (Guideline Ref ID MORA2005 [977])	No outcomes of interest
Moreira Guimaraes MM, Bartolomeu Greco D, Ingles Garces AH, de Oliveira ARJ, Bastos Foscolo R, de Campos Machado LJ. Coronary heart disease risk assessment in HIV-infected patients: a comparison of Framingham, PROCAM and SCORE risk assessment functions. International Journal of Clinical Practice. 2010; 64(6):739-745. (Guideline Ref ID MOREIRA2010 [978])	Wrong study design (cross sectional). Wrong population (not from England or Wales)
Murphy TP, Dhangana R, Pencina MJ, D'Agostino RBS. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis. 2012; 220(1):160-167. (Guideline Ref ID MURPHY2012 [992])	Wrong population (not from England or Wales)
Murphy TP, Dhangana R, Pencina MJ, Zafar AM, D'Agostino RB. Performance of current guidelines for coronary heart disease prevention: optimal use of the Framingham-based risk assessment. Atherosclerosis. 2011; 216(2):452-457. (Guideline Ref ID MURPHY2011 [993])	Wrong population (not from England or Wales)
Nasir K, Budoff MJ, Muntendam P, Nordestgaard BG, Falk E, Fuster V. Bioimage study: Novel biomarker panel (cardioscore) for the prediction of first major cardiovascular events across the full range of framingham risk scores. Circulation. 2012; 126(21 SUPPL. 1). (Guideline Ref ID NASIR2012A [1001])	Conference abstract
Neuhauser HK, Ellert U, Kurth BM. A comparison of Framingham and SCORE-based cardiovascular risk estimates in participants of the German National Health Interview and Examination Survey 1998. European Journal of Cardiovascular Prevention and Rehabilitation. 2005; 12(5):442-450. (Guideline Ref ID NEUHAUSER2005 [1016])	Wrong population (not from England or Wales)
O'Seaghdha CM, Lyass A, Massaro JM, Meigs JB, Coresh J, D'Agostino RBS et al. A risk score for chronic kidney disease in the general population. American Journal of Medicine. 2012; 125(3):270-277. (Guideline Ref ID OSEAGHDHA2012 [1037])	Wrong index test (risk core for incident chronic kidney disease)
Og OD, Byrne S, Loughrey M, Browne G, Perry I, Sahm L. Comparison of screening tools for calculating risk of cardiovascular disease in an Irish setting. International Journal of Pharmacy Practice. 2011; 19:47. (Guideline Ref ID OG2011 [1040])	Conference abstract
Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL et al. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. Journal of the American College of Cardiology. 2011; 57(18):1838-1845. (Guideline Ref ID OKWUOSA2011 [1046])	No outcomes of interest
Okwuosa TM, Greenland P, Lakoski SG, Ning H, Kang J, Blumenthal RS et al. Factors associated with presence and extent of coronary calcium in those predicted to be at low risk according to Framingham risk score (from the Multi-Ethnic Study of Atherosclerosis). American Journal of Cardiology. 2011; 107(6):879-885. (Guideline Ref ID OKWUOSA2011A [1045])	Wrong study design (cross-sectional)
Olga VO, Broda G, Kubinova R, Malyutina S, Pajak A, Tamosiunas A et al. SCORE performance in Central and Eastern Europe and former Soviet Union: MONICA and HAPIEE results. European Journal of Cardiovascular Prevention and Rehabilitation. 2011; 18(1 SUPPL. 1):S4. (Guideline Ref ID OLGA2011A [1047])	Conference abstract
Ovbiagele B, Liebeskind DS, Kim D, Ali LK, Pineda S, Saver JL. Prognostic value of Framingham Cardiovascular Risk Score in hospitalized stroke patients. Journal of Stroke and Cerebrovascular Diseases. 2011; 20(3):222-226. (Guideline Ref ID OVBIAGELE2011 [1063])	No outcomes of interest

Reference	Reason for exclusion
Paredes S, Rocha T, de CP, Henriques J, Harris M, Morais J. Long term cardiovascular risk models' combination - a new approach. Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE. 2009; 2009:4711-4714. (Guideline Ref ID PAREDES2009 [1069])	Conference abstract
Pencina MJ, D'Agostino RBS, Song L. Quantifying discrimination of Framingham risk functions with different survival C statistics. Statistics in Medicine. 2012; 31(15):1543-1553. (Guideline Ref ID PENCINA2012 [1077])	No outcomes of interest
Postley J, Luo Y, Wong N, Gardin J. Lifetime risk algorithm identifies more patients with carotid and femoral plaques than 10 yr or 30 yr framingham risk algorithms. Journal of the American College of Cardiology. 2012; 59(13 SUPPL. 1):E1714. (Guideline Ref ID POSTLEY2012A [1102])	Conference abstract
Price HC, Coleman RL, Stevens RJ, Holman RR. Impact of using a non-diabetes-specific risk calculator on eligibility for statin therapy in type 2 diabetes. Diabetologia. 2009; 52(3):394-397. (Guideline Ref ID PRICE2009A [1111])	No outcomes of interest
Quirke TP, Gill PS, Mant JW, Allan TF. The applicability of the Framingham coronary heart disease prediction function to black and minority ethnic groups in the UK. Heart. 2003; 89(7):785-786. (Guideline Ref ID QUIRKE2003 [1120])	No outcomes of interest
Ramirez-Rodrigo J, Moreno-Vazquez JA, Ruiz-Villaverde A, Sanchez-Caravaca MA, Lopez de la Torre-Casares M, Villaverde-Gutierrez C. A computer tool for cardiovascular risk estimation according to Framingham and SCORE equations. Journal of Evaluation in Clinical Practice. 2013; 19(2):277-284. (Guideline Ref ID RAMIREZRODRIGO2013 [1128])	Wrong population (not from England or Wales)
Reissigova J, Zvarova J. The Framingham risk function underestimated absolute coronary heart disease risk in Czech men. Methods of Information in Medicine. 2007; 46(1):43-49. (Guideline Ref ID REISSIGOVA2007 [1145])	Wrong population (not from England or Wales)
Riddell T, Wells S, Jackson R, Lee AW, Crengle S, Bramley D et al. Performance of Framingham cardiovascular risk scores by ethnic groups in New Zealand: PREDICT CVD-10. New Zealand Medical Journal. 2010; 123(1309):50-61. (Guideline Ref ID RIDDELL2010 [1150])	Wrong population (not from England or Wales)
Rodondi N, Locatelli I, Aujesky D, Butler J, Vittinghoff E, Simonsick E et al. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. PLoS ONE. 2012; 7(3):e34287. (Guideline Ref ID RODONDI2012 [1166])	Wrong population (not from England or Wales)
Ruiz-Villaverde G, Sanchez-Cano D, Ruiz-Villaverde R, Abalos-Medina GM, Ramirez-Rodrigo J, Villaverde-Gutierrez C. Agreement between Framingham-DORICA and SCORE scales in estimation of cardiovascular risk in the patients suffering from metabolic syndrome in Granada (Spain). Irish Journal of Medical Science. 2011; 180(2):351-354. (Guideline Ref ID RUIZVILLAVERDE2011 [1175])	Wrong study design (cross-sectional)
Saver BG, Hargraves JL, Mazor KM. Are population-based diabetes models useful for individual risk estimation? Journal of the American Board of Family Medicine. 2011; 24(4):399-406. (Guideline Ref ID SAVER2011 [1201])	No outcomes of interest
Scheltens T, Verschuren WMM, Boshuizen HC, Hoes AW, Zuithoff NP, Bots ML et al. Estimation of cardiovascular risk: a comparison between the Framingham and the SCORE model in people under 60 years of age. European Journal of Cardiovascular Prevention and Rehabilitation. 2008; 15(5):562-566. (Guideline Ref ID SCHELTENS2008 [1209])	Wrong population (not from England or Wales)
Schofield P, Chen R, Crichton N. Methods for assessing cardiovascular disease risk in a UK black population. Heart. 2012; 98(18):1373-1377. (Guideline Ref ID SCHOFIELD2012 [1215])	Wrong study design (cross-sectional)
Sehestedt T, Jeppesen J, Hansen TW, Rasmussen S, Wachtell K, Ibsen H et al. Risk stratification with the risk chart from the European Society of Hypertension compared with SCORE in the general population. Journal of Hypertension. 2009; 27(12):2351-2357. (Guideline Ref ID SEHESTEDT2009 [1225])	Wrong index test (SCORE)

Reference	Reason for exclusion
Sehestedt T, Jeppesen J, Hansen TW, Rasmussen S, Wachtell K, Ibsen H et al. Thresholds for pulse wave velocity, urine albumin creatinine ratio and left ventricular mass index using SCORE, Framingham and ESH/ESC risk charts. Journal of Hypertension. 2012; 30(10):1928-1936. (Guideline Ref ID SEHESTEDT2012 [1226])	No outcomes of interest
Sheridan S, Pignone M, Mulrow C. Framingham-based tools to calculate the global risk of coronary heart disease: a systematic review of tools for clinicians. Journal of General Internal Medicine. 2003; 18(12):1039-1052. (Guideline Ref ID SHERIDAN2003 [1251])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Singh M. Framingham equations overestimate risk of coronary heart disease mortality in British males. Evidence-Based Healthcare. 2004; 8(3):131-132. (Guideline Ref ID SINGH2004 [1268])	Narrative commentary
Siontis GCM, Tzoulaki I, Siontis KC, Ioannidis JPA. Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ. 2012; 344:e3318. (Guideline Ref ID SIONTIS2012 [1274])	Meta-analysis; inclusion criteria different from review protocol (includes ASSIGN, SCORE and PROCAM)
Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001; 44(2):156-163. (Guideline Ref ID STRATTON2001 [1305])	No outcomes of interest
Sujata G, Tiwari P, Bhansali A. Cardiovascular risk assessment using framingham risk equation in newly diagnosed type 2 diabetic indian patients. Value in Health. 2012; 15(7):A365. (Guideline Ref ID SUJATA2012 [1307])	Conference abstract
Suka M, Sugimori H, Yoshida K. Validity of the Framingham risk model applied to Japanese men. Methods of Information in Medicine. 2002; 41(3):213-215. (Guideline Ref ID SUKA2002 [1308])	Wrong population (not from England or Wales)
Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, St Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. Liver International. 2012; 32(6):945-950. (Guideline Ref ID TREEPRASERTSUK2012 [1347])	No outcomes of interest
Tunstall-Pedoe H, Woodward M. Unifactorial versus multifactorial risk - How single risk factors perform compared with Framingham and ASSIGN cardiovascular risk scores: The SHHEC study. European Heart Journal. 2009; 30:969. (Guideline Ref ID TUNSTALLPEDOE2009 [1357])	Conference abstract
Ulmer H, Kollerits B, Kelleher C, Diem G, Concin H. Predictive accuracy of the SCORE risk function for cardiovascular disease in clinical practice: a prospective evaluation of 44 649 Austrian men and women. European Journal of Cardiovascular Prevention and Rehabilitation. 2005; 12(5):433-441. (Guideline Ref ID ULMER2005 [1361])	Wrong index test (SCORE)
Uthoff H, Staub D, Socrates T, Meyerhans A, Bundi B, Schmid HP et al. PROCAM-, FRAMINGHAM-, SCORE- and SMART-risk score for predicting cardiovascular morbidity and mortality in patients with overt atherosclerosis. VASA Zeitschrift Fur Gefasskrankheiten. 2010; 39(4):325-333. (Guideline Ref ID UTHOFF2010 [1365])	Wrong population (not from England or Wales)
van der Heijden AAWA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes Care. 2009; 32(11):2094-2098. (Guideline Ref ID VANDERHEIJDEN2009 [1370])	Wrong population (not from England or Wales)
van Dieren S, Peelen LM, Nothlings U, van der Schouw YT, Rutten GEHM, Spijkerman AMW et al. External validation of the UK Prospective Diabetes Study (UKPDS) risk engine in patients with type 2 diabetes. Diabetologia. 2011; 54(2):264-270. (Guideline Ref ID VANDIEREN2011 [1372])	Wrong population (not from England or Wales)

Reference	Reason for exclusion
van Dis I, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. European Journal of Cardiovascular Prevention and Rehabilitation. 2010; 17(2):244-249. (Guideline Ref ID VANDIS2010 [1373])	Wrong index test (SCORE)
van DS, Beulens JWJ, Kengne AP, Peelen LM, Rutten GEHM, Woodward M et al. Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: A systematic review. Heart. 2012; 98(5):360-369. (Guideline Ref ID VAN2012[1371])	Systematic review, relevant studies included
Vergnaud AC, Bertrais S, Galan P, Hercberg S, Czernichow S. Ten-year risk prediction in French men using the Framingham coronary score: results from the national SU.VI.MAX cohort. Preventive Medicine. 2008; 47(1):61-65. (Guideline Ref ID VERGNAUD2008 [1376])	Wrong population (not from England or Wales)
Villines TC, Taylor AJ. Multi-ethnic study of atherosclerosis arterial age versus framingham 10-year or lifetime cardiovascular risk. American Journal of Cardiology. 2012; 110(11):1627-1630. (Guideline Ref ID VILLINES2012 [1383])	Wrong population (not from England or Wales)
Vrentzos GE, Papadakis JA, Ganotakis ES, Paraskevas KI, Gazi IF, Tzanakis N et al. Predicting coronary heart disease risk using the Framingham and PROCAM equations in dyslipidaemic patients without overt vascular disease. International Journal of Clinical Practice. 2007; 61(10):1643-1653. (Guideline Ref ID VRENTZOS2007 [1390])	No outcomes of interest
Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS et al. The Framingham predictive instrument in chronic kidney disease. Journal of the American College of Cardiology. 2007; 50(3):217-224. (Guideline Ref ID WEINER2007 [1420])	Wrong population (not from England or Wales)
Wijnhoud AD, Maasland L, Lingsma HF, Steyerberg EW, Koudstaal PJ, Dippel DWJ. Prediction of major vascular events in patients with transient ischemic attack or ischemic stroke: a comparison of 7 models. Stroke; a Journal of Cerebral Circulation. 2010; 41(10):2178-2185. (Guideline Ref ID WIJNHOUD2010 [1432])	Wrong population (not from England or Wales)
Willis A, Davies M, Yates T, Khunti K. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. Journal of the Royal Society of Medicine. 2012; 105(8):348-356. (Guideline Ref ID WILLIS2012 [1434])	Meta-analysis; inclusion criteria different from review protocol (includes non UK population)
Wilson PWF, Meigs JB. Cardiometabolic risk: a Framingham perspective. International Journal of Obesity. 2008; 32 Suppl 2:S17-S20. (Guideline Ref ID WILSON2008 [1437])	No outcomes of interest
Woodward M, Brindle P, Tunstall-Pedoe H, SIGN group on risk estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart. 2007; 93(2):172-176. (Guideline Ref ID WOODWARD2007 [1448])	Wrong index test (ASSIGN)
Yang,F.; Ye,J.; Pomerantz,K.; Stewart,M. Potential modification of the UKPDS risk engine and evaluation of macrovascular event rates in controlled clinical trials. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2013;6:247-256 (Guideline Ref ID YANG 2013[1458])	Wrong population (not from England or Wales)
Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012; 308(8):788-795. (Guideline Ref ID YEBOAH2012 [1459])	Wrong population (not from England or Wales)
Yoshida M, Mita T, Yamamoto R, Shimizu T, Ikeda F, Ohmura C et al. Combination of the Framingham risk score and carotid intima-media thickness improves the prediction of cardiovascular events in patients with type 2 diabetes. Diabetes Care. 2012; 35(1):178-180. (Guideline Ref ID YOSHIDA2012 [1469])	Wrong population (not from England or Wales)

Reference	Reason for exclusion
Yudkin JS, Chaturvedi N. Developing risk stratification charts for diabetic and nondiabetic subjects. Diabetic Medicine. 1999; 16(3):219-227. (Guideline Ref ID YUDKIN1999 [1473])	No outcomes of interest
Zalawadiya SK, Veeranna V, Niraj A, Panaich SS, Kommuri NVA, Jacob S et al. Comparative analysis between framingham risk score and a new biomarker-based risk score (HARM Score) for coronary heart disease mortality risk prediction. Journal of the American College of Cardiology. 2011; 57(14 SUPPL. 1):E1232. (Guideline Ref ID ZALAWADIYA2011A [1476])	Conference abstract
Zarich S, Luciano C, Hulford J, Abdullah A. Prevalence of metabolic syndrome in young patients with acute MI: does the Framingham Risk Score underestimate cardiovascular risk in this population? Diabetes and Vascular Disease Research. 2006; 3(2):103-107. (Guideline Ref ID ZARICH2006 [1479])	Wrong population (not from England or Wales)
Zgibor JC, Piatt GA, Ruppert K, Orchard TJ, Roberts MS. Deficiencies of cardiovascular risk prediction models for type 1 diabetes. Diabetes Care. 2006; 29(8):1860-1865. (Guideline Ref ID ZGIBOR2006 [1482])	Wrong population (not from England or Wales)
Zhu B, Haruyama Y, Muto T, Yamasaki A, Tarumi F. Evaluation of a community intervention program in Japan using Framingham risk score and estimated 10-year coronary heart disease risk as outcome variables: a non-randomized controlled trial. BMC Public Health. 2013; 13:219. (Guideline Ref ID ZHU2013 [1491])	No outcomes of interest

J.2 Dietary interventions

Study	Exclusion reason
Anon 1974[5]	Incorrect interventions
Anon 1999[18]	Incorrect interventions
Barzi 2003[147]	Incorrect interventions
Brouwer 2004[223]	Systematic review analyses are inadequate
Chowdhury 2012[315]	Systematic review is not relevant to review question or unclear PICO
Dalziel 2006[377]	Cost effectiveness study
Esposito 2010[478]	Systematic review is not relevant to review question or unclear PICO
Hellénius 1993[636]	CVD outcomes not reported
Hooper 2011[674]	Systematic review is not relevant to review question or unclear PICO
Howard 2006[678]	Wrong population
Hu 2002[684]	Systematic review: literature search not sufficiently rigorous
Iestra 2005[694]	Not RCT or SR
Kumbhani 2008[800]	Incorrect interventions
Li 2009[842]	Incorrect interventions
Liu 2011[855]	Incorrect interventions
Lu 2008[864]	Incorrect interventions
Lyon 1956[871]	Incorrect study design
Mannu 2013[900]	Systematic review is not relevant to review question or unclear PICO
Mas 2001[931]	Incorrect interventions
Morrison 1951[982]	Incorrect study design
Ramsden 2011[1133]	SR published in abstract form only

Rees 2013[1143]	SR published in abstract form only
Rischio and prevenzione investigators 2010[1159]	Incorrect interventions
Shang 2012[1240]	Systematic review is not relevant to review question or unclear PICO
Singh 1992[1272]	Inappropriate comparison
Singh 1992[1273]	Inappropriate comparison
Singh 1997[1270]	Inappropriate comparison
Sofi 2010[1281]	Systematic review is not relevant to review question or unclear PICO
Trichopoulou 2007[1348]	Incorrect study design
Truswell 1994[1352]	Systematic review: literature search not sufficiently rigorous
Turpeinen 1979[1358]	Crossover study
Tuttle 2008[1359]	No control group
Yang 2012[1457]	Incorrect interventions
Zhao 2007[1486]	Incorrect interventions

J.3 Foods enriched with phytosterols (plant stanols and sterols)

Reference	Reason for exclusion
Athyros 2011[116]	No relevant outcomes
Eussen 2011A[481]	No relevant outcomes and does not match review question
Martikainen 2007[925]	No relevant outcomes and does not match review question
DeMonty2011[417]	Abstract only (not a full paper) and no relevant outcomes and does not match review question
Genser 2011[547]	Abstract only (not a full paper) and no relevant outcomes and does not match review question
Genser 2012[548]	Incorrect study design (meta-analysis of case-control and cohort data)
Kesaniemi 2009[750]	Intervention does not match protocol (simvastatin plus ezetimibe) and Incorrect study design (cohort)
Lerman 2012[836]	No relevant outcomes
Marz 2011[929]	Abstract only (not a full paper) and no relevant outcomes and does not match review question
Moruisi 2006[983]	No relevant outcomes and does not match review question
Petrogianni 2012[1084]	No relevant outcomes and does not match review question
Shafiq 2010[1237]	Intervention does not match protocol (phytosterol not compared to placebo) and no relevant outcomes

J.4 Efficacy of statin therapy

Study	Exclusion reason
Aalbers 2012[48]	Not review population. Not guideline condition
Abletshauser 1999[56]	Incorrect interventions
Adamyan 2010[59]	Wrong population
Adelman 2001[60]	Abstract describing Hunt et al. 2001 analysis

Study	Exclusion reason
Aengevaeren 1997[62]	No outcomes of interest
Ageev 2006[63]	Wrong question
Ahmed 2006[66]	Outcomes not relevant (composite outcomes only)
Airan-javia 2009[69]	Wrong question
Alberton 2012[72]	Meta-analysis for adverse events
Alexopoulos 2013[73]	Post hoc analysis
Alkhenizan 2003[74]	Comment to HPS trial
Aloia 2007[78]	Not RCT or SR
Amarenco 2004[87]	Systematic review: literature search not sufficiently rigorous
Anand 2003[88]	Narrative paper
Angeli 2012[95]	Systematic review is not relevant to review question or unclear PICO
Anon 1997[14]	Wrong intervention
Anon 1999[17]	Abstract
Anon 2001[24]	Abstract
Anon 2001[22]	Comment to MIRACL trial
Anon 2001[23]	Not RCT or SR
Anon 2003[98]	Not RCT or SR
Anon 2004[28]	Clinical practice recommendations
Anon 2004[29]	Abstract of Koren et al. 2004
Anon 2004[30]	Clinical practice recommendations
Anon 2004[31]	Summary of HPS trial
Anon 2005[32]	Commentary
Anon 2006[35]	Not RCT or SR
Anon 2007[38]	Abstract
Anon 2007[36]	Abstract
Anon 2008[39]	Abstract
Arad 2005[102]	Composite outcomes only
Arampatzis 2005[103]	Outcomes not relevant (composite outcomes only). Composite outcomes only
Assmann 1999[115]	No hard outcomes
Athyros 2005[119]	Wrong population
Athyros 2010[121]	Narrative paper
Baigent 2005[131]	Systematic review: quality assessment is inadequate
Baigent 2010[130]	Systematic review: literature search not sufficiently rigorous
Baker 2002[135]	No outcomes of interest
Bakker-arkema 1997[136]	Abstract
Ballantyne 2002[137]	Abstract
Ballantyne 2004[138]	Meta-analysis for fluvastatin; single RCTs included
Bandyopadhyay 2001[141]	Review paper; inclusion criteria do not match the review protocol
Bax 2009[149]	No outcomes of interest
Behounek 1993[154]	Follow up <1 year
Beigel 1993[155]	Follow up <1 year
Beishuizen 2005[157]	No outcomes of interest

Study	Exclusion reason
Betteridge 2007[177]	No outcomes of interest
Binbrek 2006[181]	Follow up <1 year
Blauw 1997[188]	Meta-analysis for stroke only
Blumenthal 2000[191]	Review article; single RCTs included
Bo 2001[192]	Wrong population
Boekholdt 2005[197]	Meta-analysis. inclusion criteria do not match review protocol
Boekholdt 2012[196]	Systematic review: literature search not sufficiently rigorous
Bookstaver 2011[199]	Wrong question
Bookstaver 2012[200]	Wrong question
Bouter 1997[203]	Abstract
Bowman 2009[206]	Adverse events of the HPS trial (already reported)
Box 2007[208]	No outcomes of interest
Bray 2001[211]	No outcomes of interest
Briel 2008[215]	Systematic review is not relevant to review question or unclear PICO
Brilakis 2008[217]	Wrong population
Brown 2003[233]	Narrative paper
Brugts 2009[236]	Meta-analysis; single RCTs included
Bucher 1998[238]	Meta-analysis. only one outcome (stroke)
Bucher 1998[240]	Narrative paper
Bucher 1999[241]	Systematic review: quality assessment is inadequate
Buchwald 1996[244]	Systematic review: quality assessment is inadequate
Bukkapatnam 2010[247]	Systematic review; single RCTs included
Bulbulia 2011[248]	Longer follow up (11 years) of the HPS trial
Bushnell 2004[255]	No outcomes of interest
Calza 2008[259]	Wrong population
Campese 2000[260]	Abstract
Cannon 2006[266]	Meta-analysis; RCTs included in our analysis
Capurso 1992[269]	Follow up <1 year
Carter 2010[280]	Narrative review on rosuvastatin
Caso 2007[283]	Inappropriate comparison. Incorrect interventions
Chan 1996[293]	Wrong population
Chan 2007[292]	No outcomes of interest
Chan 2011[290]	Meta-analysis on high dose statins (RCTs included in our analysis)
Chang 2011[297]	Post-intervention study
Chatley 2007[299]	Incorrect interventions
Chen 2012[301]	Meta-analysis; single RCTs included
Cheng 2001[302]	Non-English population
Cherry 2009[304]	Narrative review
Cheung 2004[305]	Meta-analysis; RCTs included in our analysis
Chhatriwalla 2006[307]	No outcomes of interest
Chi 2007[308]	Not randomised
Cholesterol treatment trialists' (ctt) collaborators 2008[309]	Systematic review: quality assessment is inadequate

Study	Exclusion reason
Chong 2002[311]	Meta-analysis; single RCTs included
Chopra 2012[312]	Follow up <1 year
Chou 2008[313]	Follow up <1 year
Choudhry 2011[314]	Incorrect interventions
Clearfield 2001[323]	Incorrect interventions
Clearfield 2006[322]	Narrative review
Colhoun 2004[329]	Abstract of Colhoun 2004
Colhoun 2004[333]	Abstract of Colhoun 2004
Collier 2011[335]	Wrong population
Collins 2002[340]	Conference report
Correia 2003[351]	Follow up <1 year
Corsini 2003[352]	Narrative review
Corti 2005[354]	No outcomes of interest
Corvol 2003[355]	Meta-analysis on stroke; statin and non-statin therapy
Costa 2006[356]	Meta-analysis; RCTs included in our analysis
Cowell 2005[358]	Wrong population
Croom 2005[361]	Review on atorvastatin; single RCTs included
Crouse 1993[364]	Abstract
Crouse 1997[363]	Meta-analysis; inclusion criteria different from review protocol
Cui 2009[367]	No outcomes of interest
Cui 2010[366]	Paper evaluated risk factors for development of both first and subsequent MI events
Dagli 2007[375]	Wrong intervention
Danik 2012[380]	Abstract
Davidson 1997[381]	Wrong intervention
De caterina 2010[392]	Systematic review is not relevant to review question or unclear PICO
De denus 2004[393]	Meta-analysis; inclusion criteria different from review protocol
De lemos 2004[397]	Narrative summary of the A-Z trial
De lorenzo 2009[399]	Protocol only
De lorgeril 2012[406]	Systematic review is not relevant to review question or unclear PICO
Delahoy 2009[414]	Meta-analysis; RCTs included in our analysis
Dembowski 2009[416]	Narrative review
Derosa 2009[426]	Inappropriate comparison
Desilvey 2008[427]	Narrative paper
Di mascio 2000[430]	Meta-analysis; includes all cholesterol lowering therapies and diet
Dickinson 2007[433]	Wrong population
Doggrell 2006[435]	Narrative review
Domanski 2007[436]	Wrong population
Domanski 2008[437]	Wrong population
Downs 1993[443]	Narrative paper
Downs 1998[442]	Wrong intervention
Ebrahim 1999[451]	Systematic review: quality assessment is inadequate
Edmundowicz 2000[453]	Abstract

Study	Exclusion reason
Eisenbarth 2005[457]	Narrative review
Emberson 2007[463]	Analysis of HPS trial; results already reported
Enajat 2009[466]	Wrong population
Erickson 2003[470]	Follow up <1 year
Eriksson 2011[474]	Wrong comparison
Eriksson 2011[473]	Follow up <1 year
Faergeman 1995[486]	Non English publication
Faergeman 2006[485]	Non-English publication
Farmer 2009[489]	No outcomes of interest
Fedacko 2009[491]	Inappropriate comparison
Fedacko 2009[492]	Inappropriate comparison
Fedacko 2009[493]	Inappropriate comparison
Fellstrom 2003[496]	Wrong population
Fellstrom 2009[497]	Wrong population, patients on dialysis
Fink 2012[500]	Systematic review on screening. monitoring and treatment of CKD
Fleg 2008[503]	No outcomes of interest
Fonarow 2008[507]	Wrong population
Ford 2007[508]	Longer follow up of the WOSCOPS trial (included)
Forst 2007[509]	Wrong question
Fukunami 2009[521]	Wrong question
Fulcher 2011[522]	Systematic review: quality assessment is inadequate
Furberg 1994[524]	Wrong intervention
Furberg 1995[527]	Less than minimum duration. Pooled data from 2 trials: PLAC I and PLAC 2
Game 2003[534]	Comment to the HPS trial
Gaziano 1999[542]	Narrative review
Glueck 2011[559]	Incorrect interventions
Glynn 2009[560]	Incorrect interventions
Goldberger 2006[564]	Not randomised
Goodwin 1998[572]	Overview of the LIPID trial
Gotto 2000[575]	Wrong intervention
Gould 1998[576]	Meta-analysis including non-statin therapy and diet
Gresser 2004[582]	Review on atorvastatin
Gullestad 2012[594]	Wrong population
Gullestad 2012[595]	Wrong population
Gupta 2011[597]	Cox regression analysis
Gutierrez 2012[599]	Meta-analysis in secondary prevention only; RCTs included in our analysis
Haffner 1997[603]	Comment to the 4S trial
Haffner 1999[604]	Post-hoc analysis of the 4S trial
Han 2009[611]	Inappropriate comparison
Hankey 2000[614]	Abstract
Heart protection study collaborative group 2007[630]	Wrong population
Hebert 1997[633]	Narrative review

Study	Exclusion reason
Herrington 2002[642]	Not randomised
Hiro 2009[653]	Wrong intervention
Hjalmarson 2008[656]	Not guideline condition
Hjelstuen 2007[657]	Wrong population
Holdaas 2003[662]	Wrong population
Holdaas 2007[664]	SR included studies <1 year
Holdaas 2011[663]	Wrong population, patients on dialysis
Holman 2009[666]	Incorrect interventions
Hongo 2008[670]	Incorrect interventions
Horiuchi 2004[676]	Cohort study
Houslay 2006[677]	Wrong population
Howard 2009[679]	No outcomes of interest
Hsu 1995[682]	Narrative review
Hunninghake 1997[685]	Abstract
Ichihara 2005[693]	No outcomes of interest
Insull 2001[696]	Incorrect interventions
Ishikawa 2005[699]	No outcomes of interest
Jain 2012[708]	Systematic review: quality assessment is inadequate
Jardine 2004[709]	Wrong population (renal transplant)
Jha 2009[712]	Abstract of Ridker 2008 (included)
Jimenez 1999[713]	Abstract
John 1995[716]	Non-English language
Jones 2005[721]	Follow up <1 year
Kanorski? sg 2007[734]	Non-English publication
Karam 2008[735]	Abstract of Amarenco et al 2006
Kaski 2011[739]	Narrative paper
Kausar 2002[741]	Narrative review
Keane 2001[742]	Wrong population
Keech 1991[743]	Abstract
Keech 1999[744]	Abstract
Kendrick 2010[748]	Wrong intervention
Khush 2004[757]	Narrative review
Kizer 2010[764]	Meta-regression analysis; RCTs included in our analysis
Kjekshus 1995[767]	Subgroup analysis of the 4S trial
Kjekshus 1997[768]	Subgroup analysis (heart failure) of the 4S trial
Kjekshus 2005[766]	Wrong population
Kjekshus 2007[765]	Wrong population
Kobashigawa 2005[773]	Wrong population
Kong 1997[779]	Meta-analysis including non-RCTs
Koren 2009[783]	Post-hoc study
Kostis 2011[788]	Systematic review: quality assessment is inadequate
Kostis 2012[789]	Non-English publication
Krone 2003[793]	Non-English publication

Study	Exclusion reason
Kubler 2003[795]	Non-English publication
Kulbertus 2002[796]	Non-English publication
Lakhan 2010[806]	Systematic review on stroke. including non-RCTs and non-statin therapy
Laloux 2003[807]	Narrative review
Larosa 1999[812]	Meta-analysis; RCTs included in our analysis
Larosa 2010[810]	Post-hoc analysis of TNT trial (TNT trial results already reported elsewhere)
Laskey 2010[813]	Systematic review: quality assessment is inadequate
Lavigne 2011[816]	Systematic review: literature search not sufficiently rigorous
Law 2003[819]	Systematic review: quality assessment is inadequate
Lemos 2005[828]	Wrong question
Lemstra 2012[830]	Wrong question
Li 2011[843]	Wrong question
Liakopoulos 2012[844]	Wrong question
Lindgren 2010[852]	Health economic study
Lizhen 2011[856]	Incorrect interventions
Logacheva 2005[860]	Non-English language
Luijendijk 2013[865]	No outcomes of interest
Luo 2012[868]	Narrative review
Luvai 2012[870]	Narrative review
Ma 2012[872]	Wrong question
Mabuchi 2007[876]	Incorrect interventions
Mabuchi 2009[875]	Incorrect interventions
Macdonald 1998[879]	Narrative review
Maggioni 2009[884]	Wrong population
Maitland-van der zee 2007[887]	Wrong question
Makuuchi 2005[889]	Wrong population
Mancini 1995[891]	Non-English publication
Mannacio 2008[893]	Follow up <1 year
Manzato 1994[905]	Letter
Mareev 2008[912]	Non-English language
Mareev 2008[914]	Non-English publication
Mareev 2010[913]	Non-English publication
Maritz 2002[918]	Narrative review
Marrs 2010[920]	Wrong population
Mârz 2004[928]	Non-English publication
Mazzu 1998[936]	Wrong population
Meaney 2009[951]	No outcomes of interest
Mehta 2007[952]	Follow up <1 year
Miettinen 1997[958]	Narrative of RCT included in review
Mihaylova 2012[959]	Systematic review: quality assessment is inadequate
Mills 2011[960]	Meta-analysis including lovastatin and pitavastatin
Mills 2011[961]	Network meta-analysis including lovastatin and pitavastatin

Study	Exclusion reason
Minematsu 2005[964]	Abstract
Mizuguchi 2008[965]	No outcomes of interest
Mok 2009[967]	Not guideline condition
Moore 2007[973]	SR included studies <1 year
Mora 2011[975]	Cox proportional hazards model
Mora 2012[976]	Determination of risk in the TNT trial (results reported elsewhere)
Mori 2009[980]	Follow up <1 year
Mulders 2011[988]	Post hoc analysis
Mulders 2012[989]	Cohort study
Naji 2009[996]	non-RCT
Navaneethan 2009[1011]	SR included studies <1 year follow-up
Nellemann 2007[1013]	Follow up <1 year
Neverov 1997[1017]	Narrative review
Oosterhof 2011[1055]	Health economic study
Ose 2000[1060]	Follow up <1 year
Ostadal 2010[1062]	Follow-up < 1 year
Owen 2005[1064]	Abstract of Colhoun 2004
Palmer 2012[1065]	SR included studies <1 year follow-up
Palmer 2012[1068]	SR included studies <1 year follow-up
Pedersen 1996[1072]	Safety data of the 4S trial reported elsewhere
Pedersen 2000[1076]	Longer follow up (8 years) of the 4S trial; observational study
Pedersen 2010[1073]	Post-hoc analysis of IDEAL trial (original trial included)
Perez-castrillon 2008[1080]	Wrong question
Perez-castrillon 2009[1081]	Wrong question
Petretta 2010[1083]	Systematic review: literature search not sufficiently rigorous
Petronio 2005[1085]	Wrong population
Pignone 2000[1091]	Meta-analysis including non-statin therapy
Plehn 1998[1097]	Abstract
Plehn 1998[1098]	Abstract of a full paper (Plehn et al. 1999)
Poulter 2006[1103]	Abstract
Preiss 2011[1109]	Meta-analysis; RCTs included in our analysis
Preiss 2011[1106]	Systematic review: quality assessment is inadequate
Preston 2007[1110]	Wrong population
Probstfield 1995[1112]	Wrong intervention
Pyarala 2004[1115]	Subgroup analysis of the 4S trial for metabolic syndrome
Pyorala 1995[1116]	Post hoc analysis
Rahimi 2012[1123]	Meta-analysis; inclusion criteria different from review protocol
Ramesh prasad 2012[1126]	Comment
Ramesh prasad 2012[1127]	Comment
Ramjee 2011[1130]	Comment
Ray 2005[1140]	Results of the PROVE IT-TIMI 22 trial already included (Cannon 2004)
Ray 2010[1141]	Meta-analysis for primary prevention only; RCTs included in our analysis
Reinhart 2012[1144]	Wrong question

Study	Exclusion reason
Rembold 1996[1146]	Meta-analysis including non-statin therapy and diet
Ridker 2005[1151]	Sub group analysis of PROVE-IT TIMI 22 trial (population not relevant)
Ross 1999[1169]	Meta-analysis including regression or restenosis trails
Rossebø 2008[1170]	Wrong intervention
Russell 2001[1177]	Wrong question
Saia 2004[1186]	Subgroup analysis of LIPS trial (population not relevant)
Sasaki 2000[1197]	Abstract
Sasaki 2003[1194]	Data not reported in appropriate format
Sasaki 2008[1195]	No outcomes of interest
Sattar 2010[1200]	Systematic review: quality assessment is inadequate
Sawara 2008[1202]	No outcomes of interest
Sawayama 2006[1203]	Wrong comparison
Schaars 2008[1205]	Incorrect interventions
Scheen 1999[1207]	Non-English publication
Scheen 2006[1208]	Non-English publication
Schiattarella 2012[1210]	Narrative review
Schouten 2011[1216]	Wrong question
Schouten 2011[1217]	Wrong question
Schouten 2011[1218]	Wrong question
Schwartz 2001[1219]	Follow up <1 year
Seed 1997[1223]	Abstract
Seehusen 2011[1224]	Narrative review
Seki 2008[1227]	Wrong question
Serruys 2002[1228]	Not guideline condition
Sever 2005[1236]	Wrong population
Sever 2008[1235]	Wrong population
Shaughnessy 1995[1243]	Comment to the 4S trial
Shepherd 1996[1248]	Abstract
Shepherd 2006[1246]	Narrative on RCT
Shimizu 2005[1252]	Not a RCT
Shroufi 2010[1253]	Wrong question
Shurraw 2006[1255]	Review including dialysis population
Simes 1995[1259]	Review protocol
Simes 1999[1257]	Abstract
Simpson.rj 2011[1265]	Non-RCT
Skoloudik 2007[1276]	Incorrect interventions
Slejko 2011[1279]	Wrong question
Spector 2011[1287]	Meta-analysis; RCTs included in our analysis
Squizzato 2011[1289]	Wrong population
Squizzato 2011[1290]	Wrong population
Stegmayr 2005[1292]	Wrong population; 77% patients on dialysis
Stewart 2000[1299]	Wrong question
Stewart 2005[1300]	Incorrect interventions. Evaluated the association between WBC count

Study	Exclusion reason
	and coronary heart disease mortality
Stone 2005[1302]	Wrong comparison
Strandberg 2009[1303]	Post-hoc analysis of IDEAL trial (original trial included)
Takagi 2012[1312]	Wrong population (heart failure)
Tavazzi 2008[1315]	Wrong population
Taylor 2011[1320]	SR included studies <1year follow-up
Tekin 2008[1321]	Non-RCT
Thomas 2009[1327]	Comment
Thomas 2010[1328]	Narrative review
Tognoni 2008[1333]	Wrong population
Tonelli 2011[1335]	SR included drug not included in our protocol
Tonkin 1998[1338]	Abstract
Tonkin 2000[1339]	Abstract
Tonkin 2000[1340]	Subgroup analysis by type of disease (unstable angina and MI)
Tonolo 2006[1344]	Wrong question
Toth 2011[1345]	Expert opinion
Truong 2011[1351]	Narrative on RCT
Tsai 2008[1353]	Wrong population
Ukinc 2009[1360]	Non-RCT
Upadhyay 2012[1364]	Systematic review including ezetimibe
Vale 2011[1366]	Systematic review: quality assessment is inadequate
Van boven 1996[1367]	No outcomes of interest
Van der elst 2003[1368]	Meta-analysis including non-statin therapy
Van der harst 2005[1369]	No outcomes of interest
Vergouwen 2009[1377]	No outcomes of interest
Vigen 2005[1379]	Wrong comparison
Vijan 2004[1380]	Meta-analysis including non-statin therapy
Villasis-keever 2010[1382]	Systematic review: quality assessment is inadequate
Vrecer 2003[1389]	SR included lovastatin and non-English language studies
Vrtovec 2008[1391]	Wrong population
Vulic 1999[1393]	Wrong population
Wada 2005[1394]	Non-English language
Wang 2009[1402]	Non-English language
Wanner 2005[1404]	Wrong population
Wardle 1996[1409]	Wrong question
Warshafsky 1999[1411]	Meta-analysis including lovastatin
Wasielewski 2002[1412]	Non-English publication
Wee 2008[1418]	Wrong comparison
Wenke 2005[1422]	Dosage not reported
Westhuyzen 2001[1424]	Wrong population
White 1998[1428]	Abstract
White 1999[1425]	Abstract
Whitney 1999[1429]	Narrative on RCT

Study	Exclusion reason
Williams 2009[1433]	No outcomes of interest
Wilt 2004[1438]	SR included cerivastatin and lovastatin
Winchester 2010[1439]	Wrong question
Winkler 2009[1440]	Wrong question
Wu 2007[1450]	Non-English publication
Xu 2007[1451]	Wrong population
Xu 2010[1452]	Wrong population
Yamada 2007[1453]	No outcomes of interest
Yamagami 2008[1455]	No outcomes of interest
Yamanaka 2005[1456]	Wrong intervention
Yee 1998[1460]	Systematic review with different inclusion criteria
Yogo 2013[1462]	No outcomes of interest
Yokoyama 2005[1464]	No outcomes of interest
Yonemura 2005[1467]	No outcomes of interest
Yonemura 2009[1468]	Incorrect interventions
Young 2007[1471]	Incorrect interventions
Yu-an 1998[1472]	Abstract
Zeng 2005[1481]	Wrong population
Zhang 2010[1484]	Wrong population
Zhao 2007[1488]	No outcomes of interest
Zhao 2009[1485]	Design study (results not yet published)
Ziakas 1999[1492]	Abstract

J.5 Adherence to statin therapy

Study	Exclusion reason
Aalbers 2012[48]	non systematic review article
Aloia 2007[78]	not relevant does not answer the clinical question
Bookstaver 2011[199]	abstract. the full paper has been included
Choudhry 2011[314]	irrelevant does not answer the clinical question - no intervention used to improve adherance
Fedacko 2009[491]	no relevant outcomes are stated
Fedacko 2009[492]	abstract
Fedacko 2009[493]	abstract - same study as fedacko2009A
Glueck 2011[559]	results from an open lable study. the paper discusses the methodology of the ideal RCT
Lemstra 2012[830]	meta analysis of risk indicators of non adherance to statin therapy
Lizhen 2011[856]	abstract
Mabuchi 2007[876]	no relevant outcomes
Mabuchi 2009[875]	abstract and no relevant outcomes
Reinhart 2012[1144]	ystematic review. all relevant papers have alreay been included in this review

Schaars 2008[1205]	non systematic reviews and no relevant outcomes
Slejko 2011[1279]	abstract and irrelevant topic

J.6 Statins: predictors of adverse events

Paper	Reason for exclusion
Statin use and the risk of developing diabetes. Study confirms a link, but does the risk outweigh the benefits? Johns Hopkins Medical Letter, Health After 50. 2012; 24(2):1-2. (Guideline Ref ID ANON2012 [41])	Narrative
Statin use linked to increased risk of diabetes in older women. Risk of type 2 diabetes in postmenopausal women may be up to 48 percent higher than in women who do not use the cholesterol-lowering drugs, but the jury tilts in favor of continuing medication. Duke Medicine Health News. 2012; 18(4):4-5. (Guideline Ref ID ANON2012A [42])	Narrative
Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. Expert Opinion on Drug Safety. 2011; 10(3):373-387. (Guideline Ref ID ABD2011 [51])	Review
Abdulrazzaq HA, Sulaiman SAS. Prediction of renal impairment induced by statin therapy in cardiac outpatients. International Journal of Pharmacy and Pharmaceutical Sciences. 2012; 4(SUPPL.1):371-373. (Guideline Ref ID ABDULRAZZAQ2012A [53])	Retrospective cohort
Ahn SC. Neuromuscular complications of statins. Physical Medicine and Rehabilitation Clinics of North America. 2008; 19(1):47-59. (Guideline Ref ID AHN2008 [68])	Review
Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: An indirect comparison meta-analysis. Quarterly Journal of Medicine. 2012; 105(2):145-157. (Guideline Ref ID ALBERTON2012 [72])	MA – incidence of adverse events
Alsheikh-Ali AA, Abourjaily HM, Karas RH. Risk of adverse events with concomitant use of atorvastatin or simvastatin and glucose-lowering drugs (thiazolidinediones, metformin, sulfonylurea, insulin, and acarbose). American Journal of Cardiology. 2002; 89(11):1308-1310. (Guideline Ref ID ALSHEIKH2002 [80])	Incidence of adverse events
Alsheikh-Ali AA, Karas RH. The relationship of statins to rhabdomyolysis, malignancy, and hepatic toxicity: evidence from clinical trials. Current Atherosclerosis Reports. 2009; 11(2):100-104. (Guideline Ref ID ALSHEIKH2009 [81])	Review
Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. American Journal of Medicine. 2006; 119(5):400-409. (Guideline Ref ID ANTONS2006 [99])	Report
Avins AL, Manos MM, Ackerson L, Zhao W, Murphy R, Levin TR et al. Hepatic effects of lovastatin exposure in patients with liver disease: a retrospective cohort study. Drug Safety. 2008; 31(4):325-334. (Guideline Ref ID AVINS2008 [126])	Retrospective
Ballare M, Campanini M, Airoldi G, Zaccala G, Bertoncelli MC, Cornaglia G et al. Hepatotoxicity of hydroxy-methyl-glutaryl-coenzyme A reductase inhibitors. Minerva Gastroenterologica e Dietologica. 1992; 38(1):41-44. (Guideline Ref ID BALLARE1992 [139])	Incidence of adverse events
Bestehorn K, Smolka W, Pittrow D, Schulte H, Assmann G. Atherogenic dyslipidemia as evidenced by the lipid triad: prevalence and associated risk in statin-treated patients in ambulatory care. Current Medical Research and Opinion. 2010; 26(12):2833-2839. (Guideline Ref ID BESTEHORN2010 [174])	Retrospective
Bjornsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins:	Incidence of adverse

Paper	Reason for exclusion
reports of idiosyncratic liver injury post-marketing. Journal of Hepatology. 2012; 56(2):374-380. (Guideline Ref ID BJORNSSON2012 [185])	events
Black C, Jick H. Etiology and frequency of rhabdomyolysis. Pharmacotherapy:Journal of Human Pharmacology and Drug Therapy. 2002; 22(12):1524-1526. (Guideline Ref ID BLACK2002 [187])	Incidence of adverse events
Boccuzzi SJ, Bocanegra TS, Walker JF, Shapiro DR, Keegan ME. Long-term safety and efficacy profile of simvastatin. American Journal of Cardiology. 1991; 68(11):1127-1131. (Guideline Ref ID BOCCUZZI1991 [193])	Incidence of adverse events
Boccuzzi SJ, Keegan ME, Hirsch LJ, Shapiro DR, Plotkin DJ, Mitchel YB. Long term experience with simvastatin. Drug Investigation. 1993; 5(2):135-140. (Guideline Ref ID BOCCUZZI1993 [194])	Incidence of adverse events
Cash J, Callender ME, McDougall NI, Young IS, Nicholls DP. Statin safety and chronic liver disease. International Journal of Clinical Practice. 2008; 62(12):1831-1835. (Guideline Ref ID CASH2008 [282])	Review
Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004; 126(5):1287-1292. (Guideline Ref ID CHALASANI2004 [286])	Incidence of adverse events
Cham S, Evans MA, Denenberg JO, Golomb BA. Statin-associated muscle-related adverse effects: a case series of 354 patients. Pharmacotherapy:Journal of Human Pharmacology and Drug Therapy. 2010; 30(6):541-553. (Guideline Ref ID CHAM2010 [287])	Incidence of adverse events
Chan J, Hui RL, Levin E. Differential association between statin exposure and elevated levels of creatine kinase. Annals of Pharmacotherapy. 2005; 39(10):1611-1616. (Guideline Ref ID CHAN2005 [291])	No prognostic factors. Adverse events associated with statin use
Chew S. Statin-induced myopathy in the elderly: Part 1. Adverse Drug Reaction Bulletin. 2009;(255):981-982. (Guideline Ref ID CHEW2009A [306])	Report
Clarke AT, Johnson PCD, Hall GC, Ford I, Mills PR. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin: A retrospective cohort study using the UK general practice research database. Journal of Hepatology. 2012; 56:S528. (Guideline Ref ID CLARKE2012 [320])	Retrospective
Colbert JD, Stone JA. Statin use and the risk of incident diabetes mellitus: a review of the literature. Canadian Journal of Cardiology. 2012; 28(5):581-589. (Guideline Ref ID COLBERT2012 [327])	Review
Conforti A, Magro L, Moretti U, Scotto S, Motola D, Salvo F et al. Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. Drug Safety. 2006; 29(12):1163-1172. (Guideline Ref ID CONFORTI2006 [343])	Incidence of adverse events
Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Archives of Internal Medicine. 2012; 172(2):144-152. (Guideline Ref ID CULVER2012 [368])	Statin use versus non-statin use
Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR et al. Statin safety: an assessment using an administrative claims database. American Journal of Cardiology. 2006; 97(8A):61C-68C. (Guideline Ref ID CZIRAKY2006 [370])	Retrospective
Cziraky,Mark J.; Willey,Vincent J.; McKenney,James M.; Kamat,Siddhesh A.; Fisher,Maxine D.; Guyton,John R.; Jacobson,Terry A.; Davidson,Michael H. Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting. Journal of Clinical Lipidology. 2013; 7(2):102-108 (Guideline Ref ID CZIRAKY 2013 [371])	Incidence of adverse events
Davidson MH, Robinson JG. Safety of Aggressive Lipid Management. Journal of the American College of Cardiology. 2007; 49(17):1753-1762. (Guideline Ref ID	Review

Paper	Reason for exclusion
DAVIDSON2007A [382])	
Ekstedt M, Franzen LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. Journal of Hepatology. 2007; 47(1):135-141. (Guideline Ref ID EKSTEDT2007 [458])	Comparison of before and after statin therapy
El-Salem K, Ababneh B, Rudnicki S, Malkawi A, Alrefai A, Khader Y et al. Prevalence and risk factors of muscle complications secondary to statins. Muscle and Nerve. 2011; 44(6):877-881. (Guideline Ref ID ELSALEM2011 [459])	Case control
Enriquez JR, Pratap P, Zbilut JP, Calvin JE, Volgman AS. Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins. Gender Medicine. 2008; 5(1):53-61. (Guideline Ref ID ENRIQUEZ2008 [468])	Incidence of adverse events
Floyd JS, Heckbert SR, Weiss NS, Carrell DS, Psaty BM. Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. JAMA. 2012; 307(15):1580-1582. (Guideline Ref ID FLOYD2012 [505])	Incidence of adverse events
Fung EC, Crook MA. Statin myopathy: a lipid clinic experience on the tolerability of statin rechallenge. Cardiovascular Therapeutics. 2012; 30(5):e212-e218. (Guideline Ref ID FUNG2012 [523])	Incidence of adverse events
Gabb,G.M.; Vitry,A.; Limaye,V.; Alhami,G. Serious statin-associated myotoxicity and rhabdomyolysis in Aboriginal and Torres Strait Islanders: a case series. Internal medicine journal 2013;43(9):987-992. (Guideline Ref ID GABB2013 [528])	Incidence of adverse events
Gaist D, Garcia Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? European Journal of Clinical Pharmacology. 2001; 56(12):931-933. (Guideline Ref ID GAIST2001 [529])	Incidence of adverse events
Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology. 2001; 12(5):565-569. (Guideline Ref ID GAIST2001A [530])	Incidence of adverse events
Garcia-Rodriguez LA, Masso-Gonzalez EL, Wallander MA, Johansson S. The safety of rosuvastatin in comparison with other statins in over 100,000 statin users in UK primary care. Pharmacoepidemiology and Drug Safety. 2008; 17(10):943-952. (Guideline Ref ID GARCIA2008 [540])	Incidence of adverse events
Garcia Rodriguez LA, Herings R, Johansson S. Use of multiple international healthcare databases for the detection of rare drug-associated outcomes: a pharmacoepidemiological programme comparing rosuvastatin with other marketed statins. Pharmacoepidemiology and Drug Safety. 2010; 19(12):1218-1224. (Guideline Ref ID GARCIA2010 [539])	Incidence of adverse events
Goettsch WG, Heintjes EM, Kastelein JJP, Rabelink TJ, Johansson S, Herings RMC. Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. Pharmacoepidemiology and Drug Safety. 2006; 15(7):435-443. (Guideline Ref ID GOETTSCH2006 [561])	Incidence of adverse events
Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004; 292(21):2585-2590. (Guideline Ref ID GRAHAM2004 [579])	Combined statin-fibrate
Gujral GR, Cottrell WN, Barras M. Myalgia in patients on high-dose and low-to-moderate dose statin therapy. Journal of Pharmacy Practice and Research. 2009; 39(3):202-206. (Guideline Ref ID GUJRAL2009 [593])	Incidence of adverse events associated with statin use
Harris LJ, Thapa R, Brown M, Pabbathi S, Childress RD, Heimberg M et al. Clinical and laboratory phenotype of patients experiencing statin intolerance attributable to myalgia. Journal of Clinical Lipidology. 2011; 5(4):299-307. (Guideline Ref ID HARRIS2011 [620])	No analysis
Hedenmalm K, Alvan G, Ohagen P, Dahl ML. Muscle toxicity with statins. Pharmacoepidemiology and Drug Safety. 2010; 19(3):223-231. (Guideline Ref ID	Retrospective

Paper	Reason for exclusion
HEDENMALM2010 [634])	
Hey-Hadavi JH, Kuntze E, Luo D, Silverman P, Pittman D, Lepetri B. Tolerability of atorvastatin in a population aged > or =65 years: a retrospective pooled analysis of results from fifty randomized clinical trials. American Journal of Geriatric Pharmacotherapy. 2006; 4(2):112-122. (Guideline Ref ID HEY2006 [643])	Incidence of adverse events
Jacobson TA. Statin safety: lessons from new drug applications for marketed statins. American Journal of Cardiology. 2006; 97(8A):44C-51C. (Guideline Ref ID JACOBSON2006A [706])	Review
Kageyama S, Kitamura M, Kokan A, Kubota K, Kurata H, Matsui K et al. Comparative safety of statins in japanese patients: A short-term prospective case-cohort study (Japan statin study, JSS). Pharmacoepidemiology and Drug Safety. 2012; 21:270. (Guideline Ref ID KAGEYAMA2012 [731])	Abstract. No prognostic factors
Kaski JC. High dose statin treatment and new onset diabetes. Cardiovascular Drugs and Therapy. 2011; 25(6):571-572. (Guideline Ref ID KASKI2011 [739])	Narrative
Kasliwal R, Wilton LV, Cornelius V, Aurich-Barrera B, Shakir SAW. Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11,680 patients. Drug Safety. 2007; 30(2):157-170. (Guideline Ref ID KASLIWAL2007 [740])	Incidence of adverse events
Kiderman A, Ben-Dov IZ, Glikberg F, Ackerman Z. Declining frequency of liver enzyme abnormalities with statins: experience from general practice in Jerusalem. European Journal of Gastroenterology and Hepatology. 2008; 20(10):1002-1005. (Guideline Ref ID KIDERMAN2008 [759])	Incidence of adverse events
Levenson D. Experts confirm statins' safety but advise caution with certain patients. Report on Medical Guidelines and Outcomes Research. 2002; 13(13):1-5. (Guideline Ref ID LEVENSON2002 [837])	Report
Link E, Heath S, Matsuda F, Gut I, Lathrop M, Meade T et al. SLCO1B1 variants and statin-induced myopathy - A genomewide study. New England Journal of Medicine. 2008; 359(8):789-799. (Guideline Ref ID LINK2008 [854])	Univariate analysis
Luk AO, Yang X, Ma RC, Ng VW, Yu LW, Lau WW et al. Association of statin use and development of renal dysfunction in type 2 diabetes--the Hong Kong Diabetes Registry. Diabetes Research and Clinical Practice. 2010; 88(3):227-233. (Guideline Ref ID LUK2010 [866])	Statin use versus non-statin use
Ma T, Tien L, Fang CL, Liou YS, Jong GP. Statins and new-onset diabetes: a retrospective longitudinal cohort study. Clinical Therapeutics. 2012; 34(9):1977-1983. (Guideline Ref ID MA2012A [874])	Retrospective cohort. Statin versus non-statin
Ma T, Chang MH, Tien L, Liou YS, Jong GP. The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study. Drugs and Aging. 2012; 29(1):45-51. (Guideline Ref ID MA2012B [873])	Retrospective
Martin JE, Cavanaugh TM, Trumbull L, Bass M, Weber F, Jr., Aranda-Michel J et al. Incidence of adverse events with HMG-CoA reductase inhibitors in liver transplant patients. Clinical Transplantation. 2008; 22(1):113-119. (Guideline Ref ID MARTIN2008A [927])	Retrospective chart review
Marzoa-Rivas R, Crespo-Leiro MG, Paniagua-Marin MJ, Llinares-Garcia D, Muniz-Garcia J, Aldama-Lopez G et al. Safety of statins when response is carefully monitored: a study of 336 heart recipients. Transplantation Proceedings. 2005; 37(9):4071-4073. (Guideline Ref ID MARZOA2005 [930])	Retrospective
Molokhia M, McKeigue P, Curcin V, Majeed A. Statin induced myopathy and myalgia: time trend analysis and comparison of risk associated with statin class from 1991-2006. PLoS ONE [Electronic Resource]. 2008; 3(6):e2522. (Guideline Ref ID MOLOKHIA2008 [969])	Retrospective
Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236	Incidence of adverse events

Paper	Reason for exclusion
patients. American Journal of Cardiology. 2006; 97(1):61-67. (Guideline Ref ID NEWMAN2006 [1020])	
Nichols GA, Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clinical Therapeutics. 2007; 29(8):1761-1770. (Guideline Ref ID NICHOLS2007 [1024])	Retrospective
Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Annals of Pharmacotherapy. 2002; 36(2):288-295. (Guideline Ref ID OMAR2002 [1051])	Report
Oshima Y. Characteristics of drug-associated rhabdomyolysis: analysis of 8,610 cases reported to the U.S. Food and Drug Administration. Internal Medicine. 2011; 50(8):845-853. (Guideline Ref ID OSHIMA2011 [1061])	Retrospective
Palmer S, Craig J, Navaneethan S, Tonelli M, Pellegrini F, Strippoli G. Meta-analysis: Statin therapy to prevent death and major cardiovascular events in people with chronic kidney disease. Nephrology Dialysis Transplantation. 2012; 27((Palmer) University of Otago, Christchurch, New Zealand;(Craig) University of Sydney, Australia;(Navaneethan) Cleveland Clinic, United States;(Tonelli) University of Alberta, Edmonton, AB, Canada;(Pellegrini) Consorzio Mario Negri Sud, Italy;(Strippoli) Cochrane Renal Group, Sydney, Australia):ii121-ii122. (Guideline Ref ID PALMER2012 [1065])	Risk of adverse events associated with statin versus non-statin
Preiss D, Sattar N. Pharmacotherapy: Statins and new-onset diabetes - The important questions. Nature Reviews Cardiology. 2012; 9(4):190-192. (Guideline Ref ID PREISS2012 [1105])	Review
Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011; 305(24):2556-2564. (Guideline Ref ID PREISS2011 [1109])	Meta-analysis. No multivariate analysis
Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Current Opinion in Lipidology. 2011; 22(6):460-466. (Guideline Ref ID PREISS2011B [1108])	Review
Radcliffe KA, Campbell WW. Statin myopathy. Current Neurology and Neuroscience Reports. 2008; 8(1):66-72. (Guideline Ref ID RADCLIFFE2008 [1121])	Review
Sailler L, Pereira C, Bagheri A, Lapeyre-Mestre M, Montastruc JL, Arlet P et al. Increased exposure to statins in patients developing chronic muscle diseases: A 2-year retrospective study. Annals of the Rheumatic Diseases. 2008; 67(5):614-619. (Guideline Ref ID SAILLER2008 [1188])	Statin versus non-statin
Sakaeda T, Kadoyama K, Okuno Y. Statin-associated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. PLoS ONE [Electronic Resource]. 2011; 6(12):e28124. (Guideline Ref ID SAKAEDA2011 [1189])	Incidence of adverse events
Schech S, Graham D, Staffa J, Andrade SE, La Grenade L, Burgess M et al. Risk factors for statin-associated rhabdomyolysis. Pharmacoepidemiology and Drug Safety. 2007; 16(3):352-358. (Guideline Ref ID SCHECH2007 [1206])	Case control
Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. Circulation. 2012; 126(18):e282-e284. (Guideline Ref ID SHAH2012A [1238])	Review
Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clinical Therapeutics. 2006; 28(1):26-35. (Guideline Ref ID SILVA2006 [1256])	Statin versus non-statin comparison
Stein EA, Vidt DG, Shepherd J, Cain VA, Anzalone D, Cressman MD. Renal safety of intensive cholesterol-lowering treatment with rosuvastatin: a retrospective analysis of renal adverse events among 40,600 participants in the rosuvastatin clinical development program. Atherosclerosis. 2012; 221(2):471-477. (Guideline	Retrospective

Paper	Reason for exclusion
Ref ID STEIN2012 [1293])	
Toms TE, Smith JP, Panoulas VF, Douglas KMJ, Saratzis AN, Kitas GD. Prevalence of risk factors for statin-induced myopathy in rheumatoid arthritis patients. Musculoskeletal Care. 2010; 8(1):2-9. (Guideline Ref ID TOMS2010 [1334])	Incidence of adverse events
Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. Journal of the American College of Cardiology. 2009; 54(17):1609-1616. (Guideline Ref ID VOORA2009 [1388])	Composite outcome including any adverse event
Vu D, Murty M, McMorran M. Statins: Rhabdomyolysis and myopathy. WHO Drug Information. 2002; 16(2):130-131. (Guideline Ref ID VU2002 [1392])	Review
Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ et al. Statins, risk of diabetes, and implications on outcomes in the general population. Journal of the American College of Cardiology. 2012; 60(14):1231-1238. (Guideline Ref ID WANG2012A [1401])	Retrospective
Zhang Ls, Liu Zx, Lu W, Hu Xy. Effects of statins on the liver: clinical analysis of patients with ischemic stroke. Chinese Medical Journal. 2011; 124(6):897-900. (Guideline Ref ID ZHANG2011A [1483])	Retrospective

J.7 Fibrates for prevention of CVD

Study	Exclusion reason
Aalbers 2010[47]	Non RCT
Abbasi 2008[50]	No outcome of interest
Abourbih 2009[57]	Systematic review: quality assessment is inadequate
Acheson 1972[58]	Intervention not licensed
Agouridis 2011[64]	No outcomes of interest
Allemann 2006[75]	Systematic review: quality assessment is inadequate
Anon 1971[3]	Intervention not licensed
Anon 1971[1148]	Intervention not licensed
Anon 1980[7]	Intervention not licensed
Anon 1984[10]	Intervention not licensed
Arcavi 2004[104]	No outcomes of interest
Athyros 2002[122]	No outcomes of interest
Belcaro 1992[159]	Incorrect interventions
Berard 2010[164]	Not RCT
Berard 2011[165]	Not RCT
Betteridge 1994[176]	No outcomes of interest
Birjmohun 2005[184]	Systematic review is not relevant to review question or unclear PICO
Borghi 2004[201]	No outcomes of interest
Briel 2004[216]	Incorrect interventions
Burgess 2010[250]	No outcomes of interest
Canner 1980[262]	Intervention not licensed
Craig 1972[360]	Intervention not licensed

Davis 2011[386]	No outcomes of interest
De caterina 2010[392]	Systematic review: quality assessment is inadequate
De faire 1996[394]	No outcomes of interest
Deplanque 2011[423]	SR Abstract insufficient information for assessment
Derosa 2004[424]	Inappropriate comparison
Derosa 2009[425]	No outcomes of interest
Devendra 2010[428]	Incorrect interventions
Drury 2011[448]	No outcomes of interest
Elkeles 1998[460]	No outcomes of interest
Enger 2010[467]	Not RCT
Ericsson 1998[471]	Subgroup analysis not in protocol
Fagerberg 1998[487]	Wrong population
Farnier 2012[490]	Incorrect interventions
Fodor 2010[506]	Systematic review is not relevant to review question or unclear PICO
Foucher 2010[510]	SR Abstract insufficient information for assessment
Freeman 2006[515]	No outcomes of interest
Friedewald 2008[519]	Not question of interest
Geizerova 1979[544]	Intervention not licensed
Gholami 1998[550]	Wrong population
Goldberg 1990[562]	Incorrect interventions
Goldenberg 2008[565]	Post-intervention follow-up
Goldenberg 2009[566]	No outcomes of interest
Goldenberg 2009[567]	Post-intervention follow-up
Gould 2007[577]	Systematic review: quality assessment is inadequate
Gupta 2010[598]	Systematic review: quality assessment is inadequate
Haim 2002[606]	No outcomes of interest
Haim 2006[607]	No outcomes of interest
Hanefeld 1991[613]	Intervention not licensed
Heinonen 1994[635]	Post-intervention follow-up
Hongo 2008[670]	Incorrect interventions
Huttunen 1988[691]	No outcomes of interest
Huttunen 1991[692]	No outcomes of interest
Jafri 2009[707]	SR insufficient information for assessment
Jonas 1996[718]	Not question of interest
Jun 2010[727]	Systematic review: quality assessment is inadequate
Kaisar 2008[732]	Narrative review
Keech 2011[747]	No outcomes of interest
Klungel 2002[769]	Not RCT
Kohro 2007[774]	Not RCT
Koskinen 1992[787]	Post hoc analysis

Labreuche 2010[803]	Systematic review: quality assessment is inadequate
Lee 2011[826]	Systematic review: quality assessment is inadequate
Loomba 2010[863]	Systematic review: quality assessment is inadequate
Manktelow 2009[892]	Not guideline condition
Manninen 1983[895]	No outcomes of interest
Manninen 1988[896]	No outcomes of interest
Manninen 1989[897]	No outcomes of interest
Manninen 1992[898]	No outcomes of interest
Manttari 1997[904]	Not applicable to question
Mccullough 2011[942]	Narrative review
Mckeage 2011[946]	Narrative review
Moon 2011[971]	Narrative review
Nikkila 1984[1026]	No outcome of interest
Oliver 1972[1048]	Intervention not licensed
Pasternak 1996[1070]	No outcomes of interest
Patel 2008[1071]	Systematic review is not relevant to review question or unclear PICO
Pepine 2010[1079]	Narrative review
Ramjattan 2002[1129]	No outcomes of interest
Rubins 2001[1172]	Abstract; full study published
Rubins 2002[190]	No outcomes of interest
Ruotolo 1998[1176]	No outcomes of interest
Russell 2010[1178]	Incorrect interventions
Saha 2007[1185]	Systematic review: quality assessment is inadequate
Saha 2010[1184]	Systematic review: quality assessment is inadequate
Sano 2010[1191]	Incorrect interventions
Sasaki 2002[1198]	No outcomes of interest
Schima 2010[1211]	Systematic review: study designs inappropriate
Sharma 2009[1242]	Systematic review is not relevant to review question or unclear PICO
St john-brooks 1972[1291]	Intervention not licensed
Strandberg 1991[1304]	Incorrect interventions
Tanne 2002[1313]	Study not question of interest
Tenkanen 2006[1323]	Post-intervention follow-up
Ting 2011[1330]	Abstract, full study published
Ting 2011[1331]	Abstract, full study publishes
Ting 2011[1332]	Abstract, full study published
Tonelli 2004[1337]	Post hoc analysis
Tonkin 2012[1342]	Insufficient data reported for analysis
Widimsky 1997[1431]	Abstract, imsufficient information for assessment

J.8 Nicotinic acid for the prevention of CVD

Study	Exclusion reason
Abdel-maksoud 2008[52]	Not RCT, narrative review ordered for cross checking
Ahmed 2010[65]	Not RCT, narrative review ordered for cross checking
Anon 1989[11]	Not RCT, narrative review ordered for cross checking
Anon 2006[34]	Not RCT, narrative review ordered for cross checking
Anon 2010[40]	Not RCT, narrative review ordered for cross checking
Azen 1996[127]	Not question of interest
Berge 1991[166]	Not RCT; follow-up study beyond randomisation
Boden 2012[195]	Abstract of RCT included in review
Brown 1990[230]	Not question of interest, wrong comparison
Brown 1992[228]	Not question of interest
Brown 2001[229]	Not question of interest, wrong comparison
Bruckert 2010[235]	Not RCT, systematic review ordered for cross checking
Canner 1980[262]	Duplicate of RCT included in review
Canner 1986[261]	No longer randomised beyond 74 months
Canner 2005[264]	Not question of interest
Canner 2006[263]	Not question of interest
Carlson 1977[270]	Not question of interest
Carlson 1988[271]	Not question of interest
Davidson 2012[384]	No outcomes of interest
Davidson 2013[383]	No outcomes of interest
Devendra 2010[428]	Not question of interest
Doggrell 2006[435]	Not RCT, narrative ordered for cross checking
Drexel 2005[446]	Not RCT, narrative ordered for cross checking
Fagerberg 1998[487]	Not question of interest
Guo 2012[596]	Systematic review: quality assessment is inadequate
Guyton 2008[601]	Not question of interest, wrong comparison
Hollenberg 2002[665]	Not RCT; letter
Jun 2012[728]	Systematic review: quality assessment is inadequate
Lavigne 2013[817]	Not RCT, narrative ordered for cross checking
Lee 2005[824]	Duplicate of RCT included in review
Lewis 2012[839]	Not question of interest
Mcbride 2012[939]	Duplicate of RCT included in review
Mostaza 1997[984]	No outcomes of interest
Phan 2013[1087]	Not question of interest
Saccilotto 2012[1181]	Not RCT, protocol for systematic review
Sasaki 2002[1198]	Not question of interest
Schmermund 2010[1213]	No outcomes of interest
Scott 1975[1220]	Not RCT, narrative ordered for cross checking

Shah 2010[1239]	No outcomes of interest
Sharma 2006[1241]	Not RCT, case series
Simons 2009[1263]	Not question of interest
Sposito 1999[1288]	Not question of interest
Taylor 2009[1318]	Not question of interest, wrong comparison
Ting 2011[1331]	Wrong population
Vessby 1981[1378]	Not RCT, narrative ordered for cross checking
Whitney 2005[1430]	Not question of interest
Wise 2011[1441]	Not RCT, narrative ordered for cross checking
Zhao 1993[1487]	Not question of interest
Zhao 2004[1489]	Not question of interest, wrong comparison

J.9 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

Study	Exclusion reason
Anon 1984[9]	Outcomes not relevant (composite outcomes only)
Arntz 2000[110]	Intervention and comparison not relevant
Backes 2005[128]	Narrative review
Bell 2009[161]	Narrative review
Bell 2011[160]	Not RCT or SR
Borghi 2004[201]	Non- RCT (cohort study)
Brown 1992[228]	Comparison not relevant
Brown 1998[227]	Outcomes not relevant; wrong intervention (statin)
Brown 2009[232]	Incorrect interventions
Bucher 1998[239]	Systematic review including all cholesterol lowering treatments
Buchwald 1996[244]	Systematic review including all cholesterol lowering treatments
Devendra 2010[428]	Intervention and comparison not relevant
Dimkovic 2012[434]	Abstract only; outcomes not relevant
Eriksson 1998[475]	Outcomes not relevant
Florentin 2008[504]	Systematic review included studies with foloow-up less than 1 year
Gordon 1986[573]	Outcomes not relevant
Gross 1973[583]	Outcomes not relevant
Gupta 2010[598]	Narrative review
Guyton 2010[600]	Narrative review
Handelsman 2012[612]	Narrative review
Hoogwerf 1999[672]	Comparison not relevant
Insull 1992[695]	Post-trial follow up of LRC-CPPT
Levy 1987[838]	Narrative review
Mack 2000[880]	Outcomes not relevant

Macmahon 1986[883]	Outcomes not relevant; wrong intervention
Maher 1995[885]	Outcomes not relevant (composite outcomes only)
Moore 2007[972]	Outcomes not relevant
Morris 1994[981]	Outcomes not relevant
Ooi 2012[1054]	Systematic review with follow up less than 1 year
Patel 2008[1071]	Systematic review; outcomes not relevant
Preiss 2009[1107]	Systematic review including other cholesterol lowering treatments
Probstfield 1991[1113]	Comments to the LRC-CPPT
Robinson 2005[1164]	Systematic review including other cholesterol lowering treatments
Robinson 2009[1165]	Meta-analysis; outcomes not relevant
Stewart 1994[1298]	Outcomes not relevant (composite outcomes only)
Thomas 2010[1328]	Systematic review including other lipid lowering treatments
Tonolo 2000[1343]	Outcomes not relevant; cross-over trial
Tonolo 2006[1344]	Outcomes not relevant
Whitney 2005[1430]	Intervention and comparison not relevant
Zambon 2006[1477]	Outcomes not relevant; cross-over trial

J.10 Omega-3 fatty acid compounds for the prevention of CVD

Study	Exclusion reason
Abeywardena 2011[54]	Outcomes not relevant
Abhyankar 2002[55]	Outcomes not relevant
Agouridis 2011[64]	Outcomes not relevant
Albert 2002[70]	Incorrect study design. Nested case-control analysis
Almdahl 1993[76]	Outcomes not relevant
Alter 2011[82]	Letter
Anderson 2008[89]	Conference proceedings
Andreasen 2012[93]	Follow up <1 year
Andreassen 1997[94]	Outcomes not relevant
Anon 1999[18]	Comment to paper
Anon 1999[19]	Abstract only
Anon 2003[27]	Summary of American Heart Association recommendations
Anon 2005[33]	Meta-analysis
Anon 2013[43]	Letter
Anon 2013[45]	Meta-analysis with different inclusion criteria
Armaganijan 2011[105]	Meta-analysis
Arnesen 2001[109]	Narrative paper
Aucamp 1993[124]	Outcomes not relevant
Aung 2007[125]	Meta-analysis including other lipid lowering therapies
Bairati 1992[133]	Outcomes not relevant

Bairati 1993[134]	Outcomes not relevant
Barter 2008[146]	Review article
Bays 2009[151]	Conference abstract
Bhatnagar 2003[178]	Narrative paper
Bianconi 2011[180]	Outcomes not relevant
Blacher 2013[186]	Post-hoc analysis of SU.FOL.OM3 trial
Bowden 2009[204]	Population not relevant (end-stage renal disease)
Bowman 2012[207]	Protocol only, results not yet published
Briel 2004[216]	Meta-analysis
Briel 2009[214]	Systematic review
Brouwer 2003[222]	Population not relevant: patients with ventricular tachyarrhythmia
Brouwer 2006[225]	Population not relevant: patients with ventricular tachyarrhythmia
Brouwer 2009[224]	Meta-analysis
Brown 1999[231]	Narrative paper
Bucher 1999[241]	Systematic reiview
Bucher 2002[242]	Review article
Bucher 2002[243]	Meta-analysis
Burr 2003[251]	Not pharma preparation (dietray intervention)
Burr 2005[252]	Outcomes not relevant
Cairns 1996[257]	Follow up 18 weeks
Calo 2005[258]	Outcomes not relevant
Carroll 2002[279]	Review article
Chagan 2002[285]	Review article
Chen 2011[300]	Meta-analysis
Cheng 2008[303]	Review article
Christensen 1996[318]	Outcomes not relevant
Christensen 1998[317]	Outcomes not relevant
Cleland 2004[324]	Review article
De magalhaes carrapeiro 2009[408]	Follow up <1 year; outcomes not relevant
Dean 1996[411]	Review article
Delgado-lista 2012[415]	Systematic review
Di minno 2002[431]	Narrative paper
Donadio 1994[438]	Outcomes not relevant
Donadio 1999[439]	Outcomes not relevant
Donadio 2004[440]	Review article
Dragomir 2010[444]	Poster abstract
Durrington 2001[449]	Outcomes not relevant
Earnest 2012[450]	Follow up <1 year
Ebrahimi 2004[452]	Review article
Erkkila 2003[476]	Not pharma preparation (dietary)

Eslick 2009[477]	Systematic review
Eussen 2012[482]	Not pharma preparation (margarine spread)
Farbakhsh 2005[488]	Outcomes not relevant
Filion 2010[498]	Meta-analysis
Fineberg 1999[499]	Narrative paper
Friedberg 1998[518]	Meta-analysis
Friedman 2010[520]	Narrative paper
Garg 1998[541]	Narrative paper
Geelen 2005[543]	Outcomes not relevant
Geleijnse 2010[546]	Not pharma preparation (diet)
Geleijnse 2012[545]	Not pharma preparation (diet)
Ginty 2012[556]	Outcomes not relevant
Hamazaki 2004[610]	Letter
Harper 2005[619]	Systematic review
Harris 2001[621]	Review article
Harris 2004[622]	Narrative paper
Harrison 2005[623]	Narrative review
Hartweg 2008[624]	Meta-analysis with different inclusion criteria
Hensrud 1994[639]	Outcomes not relevant
Hjermann 1998[659]	Wrong intervention (food preparation)
Hogg 1996[661]	Narrative review
Holman 2009[666]	Outcomes not relevant
Holub 2004[667]	Outcomes not relevant
Hoogeveen 2012[671]	Wrong intervention (margarine spreads)
Hooper 2004[673]	Meta-analysis with different inclusion criteria
Hooper 2006[675]	Systematic review
Hu 2003[683]	Incorrect study design. Cohort study
Iso 2001[700]	Incorrect study design. Prospective cohort study
Itakura 2011[701]	Outcomes not relevant
Jenkins 2008[710]	Review article
Kasiske 2003[738]	Narrative report
Kasiske 2004[737]	Narrative report
Khawaja 2012[753]	Meta-analysis
Khosroshahi 2010[754]	Wrong population (haemodialysis)
Khoueiry 2013[755]	Wrong intervention (dietary supplement)
Kim 2009[761]	Conference abstract
Kooshki 2011[781]	Population not relevant (dialysis)
Kooshki 2011[782]	Population not relevant (dialysis)
Kromhout 2010[792]	Not pharma preparation (margarine)
Kromhout 2011[791]	Not pharma preparation (margarines)

Kruse 2013[794]	Wrong intervention (dietary supplement)
Kumar 2010[797]	Conference abstract
Kumar 2011[799]	Outcomes not relevant
Kumar 2012[798]	Outcomes not relevant
Kwak 2012[802]	Meta-analysis with different inclusion criteria
Leaf 2005[821]	Population not relevant: patients with ventricular tachyarrhythmia
Lee 2004[825]	Narrative review. Dietary intervention
Lenzi 1996[832]	Outcomes not relevant
Leon 2009[833]	Systematic review
Lok 2012[861]	Population not relevant (dialysis)
Lonn 2013[862]	Subgroup analysis of the ORIGIN trial
Mackay 2012[881]	Outcomes not relevant
Maki 2010[888]	Outcomes not relevant
Manning 2013[899]	No outcomes of interest
Manson 2012[902]	Protocol only (results not yet published)
Marchioli 2000[907]	Comment to GISSI trial
Marchioli 2001[910]	Further analysis from the GISSI trial (included)
Marchioli 2002[911]	Further analysis from the GISSI trial
Marchioli 2005[909]	Antiarrhythmic mechanism from GISSI trial (included)
Marchioli 2009[908]	Outcomes not relevant
Maresta 2002[915]	Follow up 24 hours and 6 months
Marik 2009[917]	Systematic review
Marrs 2010[920]	Review article. Population not relevant (haemodialysis)
Matsuzaki 2009[932]	Post-hoc analysis
Mauro 1992[933]	Review paper
Maysuzaki 2009[935]	Post-hoc analysis
Mcewen 2010[943]	Review article
Mcgrath 1996[945]	Outcomes not relevant
Mead 2006[948]	Systematic review
Micallef 2009[956]	Outcomes not relevant
Mori 2004[979]	Narrative papaer
Mozaffarian 2008[986]	Review
Mozaffarian 2011[987]	Systematic review
Mozaffarian 2012[985]	Population not relevant
Musa-veloso 2011[994]	Systematic review
Nestel 2001[1014]	Narrative paper
Newby 2007[1018]	Letter
Nilsen 2004[1028]	Letter
Nordoy 2002[1034]	Outcomes not relevant
O'connor 1992[1036]	Meta-analysis

Oh 2005[1041]	Clinical review
Oikawa 2009[1044]	Post-hoc analysis
Ong 2008[1052]	Review article
Origasa 2010[1057]	Outcomes not relevant
Origin 2012[1059]	Wrong comparison
Pittler 2005[1095]	Systematic review
Pletcher 2005[1100]	Review paper
Poppitt 2009[1101]	Outcomes not relevant
Pratt 2009[1104]	Design and baseline characteristics only
Rauch 2010[1137]	Poster abstract (OMEGA trial included)
Rissanen 2000[1160]	Incorrect study design. cohort study
Rizos 2011[1162]	Meta-analysis with different inclusion criteria
Rizos 2012[1163]	Wrong intervention (dietary supplement)
Robinson 2005[1164]	Systematic review
Ruxton 2004[1179]	Meta-analysis with different inclusion criteria
Saifullah 2007[1187]	Outcomes not relevant. Population not relevant (haemodialysis)
Samuel 2011[1190]	Outcomes not relevant
Saravanan 2009[1192]	Poster abstract
Saravanan 2010[1193]	Outcomes not relevant
Sasaki 2012[1196]	Outcomes not relevant
Sharma 2009[1242]	Systematic review
Singer 2003[1267]	Outcomes not relevant
Sirtori 1997[1275]	Outcomes not relevant
Skou 2001[1277]	Outcomes not relevant
Sommerfield 2007[1285]	Outcomes not relevant
Stone 2000[1301]	Comment to the GISSI trial (included)
Studer 2005[1306]	Systematic review
Szabo de edelenyi 2012[1310]	Outcomes not relevant
Taccone-gallucci 2006[1311]	Outcomes not relevant
Trikalinos 2012[1349]	Systematic review
Villani 2013[1381]	Systematic review with follow uo less than 1 year
Vlachopoulos 2013[1384]	Protocol only
Von schacky 2001[1387]	Outcomes not relevant
Von schacky 2013[1385]	Narrative paper
Wang 2004[1399]	evidence report/technology assessment. Evidence report/technology assessment
Wang 2006[1400]	Systematic review
Watanabe 2011[1413]	Outcomes not relevant
Watts 1996[1416]	Review article
Weisman 2011[1421]	Outcomes not relevant
Wong 2010[1443]	Outcomes not relevant

Woodman 2005[1447]	Review article
Yzebe 2004[1474]	Meta-analysis with different inclusion criteria
Zabat 2011[1475]	Meta-analysis with different inclusion criteria
Zampelas 2003[1478]	No outcome of interest. Narrative paper
Zhao 2009[1490]	Meta-analysis

Appendix K: Excluded economic studies

K.1 Risk assessment tools

Reference	Reason for exclusion
Wald 2011[1397]	This study was assessed as partially applicable with very serious limitations. The study looks at an intervention of a statin given with blood-pressure-lowering drugs, for which the clinical effectiveness used is much greater than the clinical review in this guideline found for statin use alone. Hypothetical costs are used for the costs of drugs and carrying out risk assessments; these do not reflect current UK costs.

K.2 Dietary interventions

Reference	Reason for exclusion
Martikainen 2011[926]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on surrogate measures which are projected to lead to reductions in clinical outcomes; the clinical review for this question did not find any evidence on that relationship or on the clinical effectiveness of these specific interventions in general, and so the GDG cannot assess whether the clinical evidence used in this analysis is reasonable.
Plans Rubio 1997[1096]	This study was assessed as not applicable. The study investigates the cost effectiveness of any hypothetical dietary intervention which reduces cholesterol by a set amount, but does not investigate any specific dietary intervention, or use real life clinical effectiveness data.
Zomer 2012[1493]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on a surrogate measure which is projected to lead to reductions in clinical outcomes; the clinical review for this question did not find any evidence on that relationship or on the clinical effectiveness of the intervention in general, and so the GDG cannot assess whether the clinical evidence used in this analysis is reasonable.

K.3 Foods enriched with phytosterols (plant stanols and sterols)

Reference	Reason for exclusion
Eussen 2011A[481]	This study was assessed as not applicable. Costs are not calculated from the perspective of the NHS and personal social services.
Gerber 2006[549]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on a surrogate measure which is projected to lead to reductions in clinical outcomes; the clinical review for this question did not find any evidence on that relationship or on the clinical effectiveness of the intervention in general, and so the GDG cannot assess whether the clinical evidence used in this analysis is reasonable.
Martikainen 2007[925]	This study was assessed as not applicable. Costs are not calculated from the perspective of the NHS and personal social services.
Phillips 2000[1089]	This study was assessed as partially applicable with very serious limitations. The analysis is based on partial and out-of-date data which do not reflect the total currently available clinical evidence or current UK treatment costs. The clinical effectiveness is based on a surrogate measure which is projected to lead to reductions in clinical outcomes. The study is less relevant to this question than

Reference	Reason for exclusion
	Gerber 2006.[549]

K.4 Efficacy of statin therapy

Reference	Reason for exclusion
Annemans 2010[97]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Ashraf 1996[112]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Athyros 2002[120]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Attanasio 2001[123]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Badia 1999[129]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Barrios 2012[143]	This study was assessed as having limited applicability and potentially serious limitations. Evidence from the UK was identified which was more applicable.
Barry 1999[145]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Beaudoin 2001[152]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Benner 2005[163]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Berto 2000[170]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Brandle 2003[210]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Buller 2003[249]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Caro 1997[274]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Caro 1999[275]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Caro 2000[277]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Caro 2003[273]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Casciano 2004[281]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
CDC Diabetes Cost-effectiveness Group 2002[284]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
National Collaborating Centre for Primary Care 2008, model C[1005]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Chan 2007[294]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Chong 2005[310]	This study was assessed as having very serious limitations. More recent evidence

Reference	Reason for exclusion
	was identified which was more applicable.
Chrisp 1992[316]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Cobiac 2012[325]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Cobos 1999[326]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Conly 2011[344]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Cook 2004[346]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Costa 2008[357]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Davies 2006[385]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Denton 2009[419]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Drummond 1993[447]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Ebrahim 1999[451]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Elliott 1999[462]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Fragoulakis 2012[511]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Gandhi 2012[537]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Ganz 2000[538]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Glasziou 2002[557]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Glick 1992[558]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Goldman 1991[568]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Grover 1999[587]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Grover 2000[589]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Grover 2001[588]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Grover 2003[591]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Grover 2008[585]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Herman 1999[640]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Herregods 2008[641]	This study was assessed as having limited applicability and very serious

Reference	Reason for exclusion
	limitations. Evidence from the UK was identified which was more applicable.
Hilleman 1999[645]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Hilleman 2000[644]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Hinzpeter 1999[646]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Hippisleycox 2000[648]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Hirsch 2005[654]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Heart Protection Study Collaborative Group 2005[629]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Heart Protection Study Collaborative Group 2006[632]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Heart Protection Study Collaborative Group 2009[631]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Huse 1998[689]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Huse 2006[690]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Ito 2001[703]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Ito 2011[704]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Johannesson 1996[714]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Johannesson 1997[715]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Jonsson 1996[724]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Jonsson 1999[723]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Jonsson 2001[722]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Kang 2009[733]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Khoury 2009[756]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Kiessling 2005[760]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Kong 1996[778]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Kongnakorn 2009[780]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lachaine 2007[804]	This study was assessed as having limited applicability and very serious

Reference	Reason for exclusion
	limitations. Evidence from the UK was identified which was more applicable.
Lafuma 2008[805]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lazar 2011[820]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Lim 2001[848]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Lindgren 2005[851]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Lindgren 2007[853]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
MacDonald 2010[878]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Maclaine 2001[882]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Mark 2008[919]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Martens 1994[922]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Moisan 1999[966]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Montouchet 2013[970]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Muls 1998[990]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Nagatakobayashi 2005[995]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Nash 2006[1000]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Ohsfeldt 2010[1042]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Ohsfeldt 2012[1043]	This study was assessed as partially applicable with potentially serious limitations. However, the GDG judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Olsson 2004[1050]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Onishi 2013[1053]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Palmer 2003[1067]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Pedersen 1996[1072]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Perreault 2000[1082]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Peura 2008[1086]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Pharoah 1996[1088]	This study was assessed as having very serious limitations. More recent evidence

Reference	Reason for exclusion
	was identified which was more applicable.
Pickin 1999[1090]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Pilote 2005[1092]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Pinto 2008[1093]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Raikou 2007[1124]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Ramsey 2008[1135]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Reckless 1996[1142]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Riviere 1997[1161]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Rosen 2010[1168]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Russell 2001[1177]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Scuffham 2004[1222]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Shepherd 2001[1244]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Simpson 2009[1266]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Simpson 2011[1265]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Slejko 2010[1278]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Smith 2003[1280]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Soini 2010[1282]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Spearman 1997[1286]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Tarragalopez 2005[1314]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Taylor 2009[1319]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.
Thanh 2012[1326]	This study was assessed as not applicable. Evidence using QALYs was identified which was more applicable.
Tonkin 2006[1341]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Tran 2007[1346]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Troche 1998[1350]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Tsevat 2001[1355]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.

Reference	Reason for exclusion
Vanhout 2001[1374]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Wagner 2009[1396]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Wagner 2009[1395]	This study was assessed as having limited applicability and very serious limitations. Evidence from the UK was identified which was more applicable.
Wilson 2003[1435]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Yeo 2000[1461]	This study was assessed as having very serious limitations. More recent evidence was identified which was more applicable.
Zechmeister 2008[1480]	This study was assessed as having very serious limitations. Evidence was identified using more applicable costs for statins.

K.5 Adherence to statin therapy

None

K.6 Statins: predictors of adverse events

None

K.7 Fibrates for the prevention of CVD

Reference	Reason for exclusion
Carrington 2008[278]	This study was assessed as partially applicable with very serious limitations. The drug costs used for both fenofibrate and statins were much higher than current UK costs, and they were assumed to be equivalent which is not the case now. It is not clear how altering these costs would affect the results of the model.
Feher 2003[494]	This study was assessed as partially applicable with very serious limitations. The drug costs used for both fenofibrate and statins are much higher than current UK costs (5–7 times and 13–25 times higher respectively), and statins are assumed to be more expensive than fenofibrate, which is not the case now. It is not clear how altering these costs would affect the results of the model.
Hay 2005[625]	This study was assessed as not applicable. This study was based on clinical effectiveness data from the VA-HIT study also reported in Nyman 2012, however the GDG judged that Nyman 2012 was of greater applicability to this review question, and therefore this study was selectively excluded.

K.8 Nicotinic acid for the prevention of CVD

Reference	Reason for exclusion
Michailov 2012[957]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on surrogate measures which are projected to lead to reductions in clinical outcomes; this is inconsistent with the results of the clinical review for this

Reference	Reason for exclusion
	question, which found no clinical benefit from nicotinic acid.
Roze 2007[1171]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on surrogate measures from 1 trial which are projected to lead to reductions in clinical outcomes; this is inconsistent with the results of the clinical review for this question, which found no clinical benefit from nicotinic acid.

K.9 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

Reference	Reason for exclusion
Martens 1989[923,924]	This study was assessed as not applicable and with very serious limitations. The clinical effectiveness is based on surrogate measures which are projected to lead to reductions in clinical outcomes; this is inconsistent with the results of the clinical review for this question, which found no clinical benefit from bile acid sequestrants. The age of the study also means that all of the costs used are out of date and inapplicable.
Simons 2010[1264]	This study was assessed as partially applicable with very serious limitations. The clinical effectiveness is based on surrogate measures which are projected to lead to reductions in clinical outcomes; this is inconsistent with the results of the clinical review for this question, which found no clinical benefit from bile acid sequestrants.

K.10 Omega-3 fatty acid compounds for the prevention of CVD

Reference	Reason for exclusion
Franzosi 2004[513]	This study was assessed as not applicable with very serious limitations. The effectiveness data is based on the Marchioli 1999 (GISSI)[906] trial, which had different clinical findings from the clinical evidence review conducted for this question. In addition this study also uses an Italian setting, and thus is less applicable than Quilici 2006.
Lamotte 2006[809]	This study was assessed as not applicable with very serious limitations. The effectiveness data is based on the Marchioli 1999 (GISSI)[906] trial, which had different clinical findings from the clinical evidence review conducted for this question. In addition this study also uses 5 non-UK settings, and thus is less applicable than Quilici 2006.
National Collaborating Centre for Primary Care 2007[1002]	This study was assessed as partially applicable with very serious limitations. The effectiveness data is based on the Marchioli 1999 (GISSI)[906] and Burr 1989 (DART1)[253] trials, which had different clinical findings from the clinical evidence review conducted for this question. In addition DART1 was a partially dietary study, which is outside the scope of this question and was not included in the clinical review.
Quilici 2006[1118,1119]	This study was assessed as partially applicable with very serious limitations. Although it uses a UK setting the effectiveness data is based on the Marchioli 1999 (GISSI)[906] trial, which had different clinical findings from the clinical evidence review conducted for this question, and hence its conclusions on cost effectiveness would be highly likely to change if the clinical evidence reviewed for this question was used instead of that from GISSI.
Schmier 2006[1214]	This study was assessed as not applicable with very serious limitations. The effectiveness data is based on the Marchioli (GISSI),[906] Nilsen 2001,[1027] Singh 1997 (IEIS)[1270] and von Schacky 1999 (SCIMO)[1386] trials, which had different clinical findings from the clinical evidence review conducted for this question.

Appendix L: Cost-effectiveness analysis: low-intensity, medium-intensity and high-intensity statin treatment for the primary and secondary prevention of CVD

L.1 Introduction

This clinical guideline updates clinical guideline 67 (CG67)[1004] (2008) and technology appraisal 94 (TA94)[1007] (2006). The cost effectiveness of statin treatment was modelled for both these publications:

- Ward et al. (2005) modelled the cost effectiveness of statin treatment versus placebo in both the primary and secondary prevention of cardiovascular disease (CVD)[1406-1408] to inform TA94. This was subsequently also published as a health technology assessment (2007).[1405]
- The National Collaborating Centre for Primary Care (NCCPC) (2008) modelled the cost effectiveness of high-intensity statin treatment against medium-intensity statin treatment in the secondary prevention of CVD[1003] as part of CG67.

Since these publications the cost of some statins in the UK has declined dramatically due to their patents expiring and the subsequent availability of generic versions. Further clinical trials have also been conducted, and more data is available on adverse events.

Chapter 11 in this guideline addresses the review question 'What is the clinical and cost effectiveness of statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?' The economic review for this question assessed 129 published economic studies, but most were found not to be applicable to the current UK situation, and none compared the cost effectiveness of low-, medium- and high-intensity statins. In addition, research by Catala-Lopez et al. (2013){CATALALOPEZ2013} has shown evidence for publication bias in economic evaluations of statins, with 0% of 48 industry-funded economic evaluations reporting neutral or unfavourable conclusions, compared to 37% of 27 non-industry-funded economic evaluations. The economic plan prioritised this question as the highest priority for original economic analysis in this guideline. Therefore original economic modelling has been conducted to answer this question.

This model follows many of the principles of the Ward and NCCPC models, but updates statin costs; separates statins into 3 intensity groups and compares the efficacy of these against each other as meta-analysed in our clinical review; and adds in consideration of adverse events.

The model looks separately at the cost effectiveness of reducing cardiovascular (CV) events in those without previous clinical evidence of CVD (primary prevention) and the cost effectiveness of reducing further CV events in those with existing CVD (secondary prevention). The same comparators are considered as options for both primary and secondary care, but these are separate questions and it is not assumed that the same comparator will necessarily be preferred for both.

In addition to statins this clinical guideline investigates the clinical and cost effectiveness of other lipid-lowering drugs, taken either instead of or in addition to statins; these are not included within this model. This guideline also studies the benefits of lifestyle interventions, including diet, exercise and smoking cessation in reducing CVD and makes recommendations on these issues. Their effects cannot be directly compared to those of statins as there have not been comparative studies, but neither is it necessary to do so, since lifestyle measures are complementary to the use of statins and can be adopted either before or alongside statin therapy. The fact that they are not included in this model should not be read as implying that statin therapy is the only available intervention to modify lipid levels; rather statin therapy was chosen for modelling because it includes several competing treatment options and the comparative cost effectiveness of these alternatives was previously unclear.

L.2 Methods

L.2.1 Model overview

L.2.1.1 Comparators

Five statins are currently available on prescription in the UK, with a total of 18 doses. (One dose – simvastatin 10 mg is also available over the counter.)

This model divides statins into 3 intensity groups, in line with the clinical review in Chapter 11, based on their ability to reduce LDL cholesterol in short-term trials[819] (see clinical review).

- Low-intensity statins: (21–29% reduction in LDL cholesterol)
  - fluvastatin 20 mg per day
  - fluvastatin 40 mg per day

  - pravastatin 10 mg per day
  - pravastatin 20 mg per day
  - pravastatin 40 mg per day
  - simvastatin 10 mg per day.
- Medium-intensity statins: (32–38% reduction in LDL cholesterol)
  - fluvastatin 80 mg per day
  - simvastatin 20 mg per day
  - simvastatin 40 mg per day
  - atorvastatin 10 mg per day
  - rosuvastatin 5 mg per day.
- High-intensity statins: (42–55% reduction in LDL cholesterol)
  - simvastatin 80 mg per day
  - atorvastatin 20 mg per day
  - atorvastatin 40 mg per day
  - atorvastatin 80 mg per day
  - rosuvastatin 10 mg per day
  - rosuvastatin 20 mg per day
  - rosuvastatin 40 mg per day.
- No treatment

The names of individual statin doses are abbreviated in the tables below by initial letter of the statin and daily dose in mg, for example, 'S10' represents simvastatin 10 mg per day.

L.2.1.2 Risk tools

Several different tools are available to calculate an individual's risk of future CV events. This model is designed to support the use of the QRISK2 tool for predicting risk in people without diabetes being considered to receive statins for primary prevention, and the UKPDS risk engine for predicting risk in people with type 2 diabetes being considered to receive statins for primary prevention. The model focused on these risk tools as they were the tools being considered most seriously by the GDG for use in risk assessment. For the GDG's recommendations on risk assessment see Chapter 6.

QRISK2 (10-year) is a CV risk tool developed by Hippisley-Cox et al.[652] based on the QRESEARCH UK primary care cohort. It estimates an individual's risk of experiencing any of fatal or non-fatal angina, MI, TIA or stroke over the following 10 years, and can be found at http://www.qrisk.org/index.php.

The UKPDS risk engine is a CV risk tool developed from the results of the UK Prospective Diabetes Study.[1297] It estimates both an individual's risk of fatal or non-fatal MI or other cardiac death and their risk of fatal or non-fatal stroke over the following 10 years, and can be found at http://www.dtu.ox.ac.uk/riskengine/. The risks given in this analysis correspond to the sum of these 2 risks, and assume that the risks do not overlap to cause double-counting.

Other risk calculators exist (for example Framingham); alternatively people can be allocated to treatment based solely on their age. See Chapter 6 for the review of risk assessment systems.

None of the tools measure what is referred to in this analysis as 'total CV risk' – that is the chance of developing any form of CVD, which we define as including peripheral artery disease (PAD) and heart failure in addition to the factors included in QRISK2. Therefore the 'CV risk' level predicted by QRISK2 is not equivalent to the same risk level predicted by UKPDS, and neither are equivalent to the 'total CV risk'. The risk levels which are equivalent in different tools vary depending on age and sex, but for

example a total 10-year CV risk of 20% in a man aged 60 is equivalent to a QRISK2 score of 13.71% and a combined UKPDS score of 7.25%.

L.2.1.3 Population

All analyses relate to the population of England and Wales. Statin interventions are investigated in 3 specific groups:

- Adults with established CVD (secondary prevention)
  - cost effectiveness assessed for the group as a whole.
- Adults without established CVD (primary prevention)
  - cost effectiveness assessed for groups with CV risk levels of 30%, 25%, 20%, 15%, 10%, 5% as measured using the QRISK2 calculator.
- Adults with type 2 diabetes without established CVD (primary prevention)
  - cost effectiveness assessed for groups with CV risk levels of 30%, 25%, 20%, 15%, 10%, 5% as measured using the UKPDS calculator.

For primary prevention we also planned to carry out additional analyses using smaller gradations of risk around wherever the threshold of cost effectiveness appeared to be (for example, if the threshold appeared to be slightly below 10% then additional analyses would be carried out at 8% and 9%).

No analyses were carried out for people with type 1 diabetes or chronic kidney disease – these populations were investigated in this guideline, but no differential effectiveness data was available to model, and no distinct risk tool appropriate to them is available.

L.2.1.4 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the NICE reference case[1010] including incremental analysis and discounting at 3.5% for both costs and health effects. A sensitivity analysis was conducted using a discount rate of 1.5% for costs and health benefits.

The base case takes a lifetime perspective (continuing to death, up to a maximum 100 years), assuming that treatment is continued and has equal efficacy throughout life.

Most clinical trials of statins have investigated effectiveness for up to 5 years, with a small number continuing for up to 10 years. Clinical effectiveness appears to continue undiminished up to 10 years. We assume that this continues throughout life – this is biologically plausible, but no trials have confirmed this. Sensitivity analyses examine shorter treatment durations.

Health state utility multipliers were found from the best available sources. They were derived from a number of studies carried out in a mixture of UK and international populations, some using patient-reported quality of life but some relying on expert assumptions. Otherwise there are no other deviations from the NICE reference case.

L.2.2 Approach to modelling

Secondary and primary prevention were investigated separately:

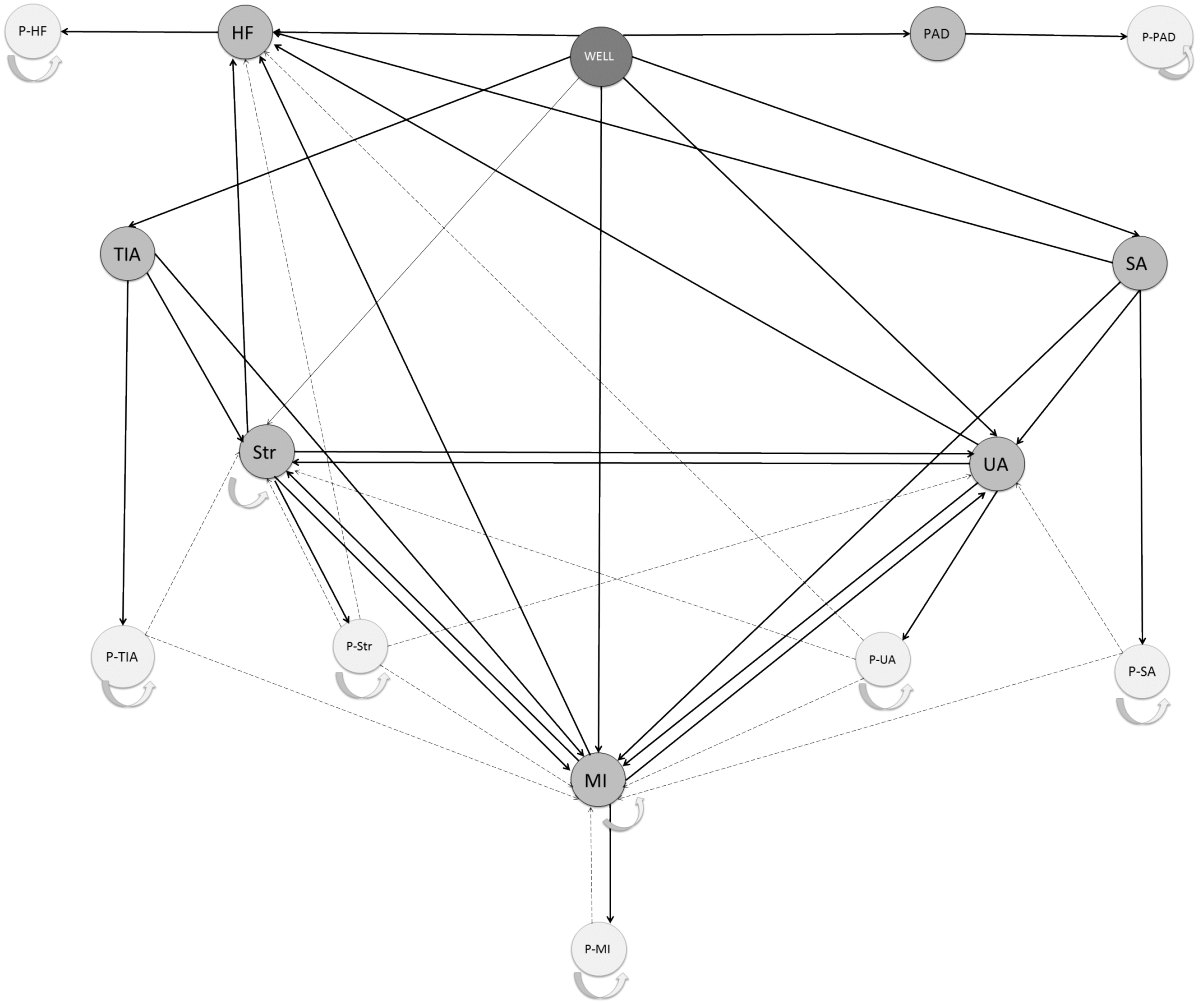
L.2.2.1 Secondary prevention

A health state transition (Markov) model was developed. The model follows a cohort of people who have just experienced their first (non-fatal) CV event. The distribution of first events varies by age and sex. They then progress through annual cycles until death or age 100.

The model included death due to any cardiovascular cause (CV death) and 7 non-fatal CV conditions: stable angina, unstable angina, myocardial infarction (heart attack – MI), transient ischaemic attack ('mini-stroke' – TIA), heart failure, and peripheral artery disease (PAD). Collectively these make up CVD, and the risk of any of these conditions occurring within 10 years is defined in this report as 'total CV risk'. We note that this is broader than some other definitions of CVD. Coronary heart disease (CHD) is defined as stable or unstable angina, MI, or cardiac death. The model also includes a state for death through other causes (non-CV death).

For each CV condition 2 health states were used in the model: an 'event' state (for example, MI), and a 'post-event' state (for example, post-MI). While it is acknowledged that some CV conditions, such as stable angina, do not present as acute 'events' but as ongoing conditions, for ease of description the onset of all newly experienced CV conditions and events are collectively referred to as 'CV events', and it is also acknowledged that some post-event states, for example post-stable angina or post-heart failure, relate to people who in practice have a continuing condition, and should not be assumed to be in recovery or free of symptomatic disease.

Figure 165: Structure of the health economic Markov model for the cost effectiveness of statins



Key: HF: heart failure; MI: myocardial infarction; P-: post-event state; PAD: peripheral artery disease; SA: stable angina; Str: stroke; TIA: transient ischaemic attack; UA: unstable angina.
The same structure applies to the primary prevention and secondary prevention models, but in the primary model all individuals start in the Well state, whereas in the secondary model all individuals start in the state representing their first CV event.

Each CV event is represented by 2 health states in the model: event (darker) for the first year in which the event occurs, and post-event (paler) for all subsequent years. Individuals automatically move from event states to the respective post-event state after 1 year, unless they instead have another CV event.
All states also have transitions to both CV death and non-CV death – these are not shown.

The standard limitations of Markov models apply to this model: that is, each member of the cohort could undergo only 1 transition per cycle (year), and so could not experience more than 1 CV event per year. There was however no limit to the number of events which can be experienced during a lifetime. Markov models also do not preserve memory of past events, and so the risk of experiencing a further stroke for someone in the post-stroke state was equal whether they had previously experienced 1 stroke or several strokes.

The memory-less condition was partially attenuated by the use of 2 states for each condition. Following each CV event individuals enter the event state for a single year and then transfer automatically to the post-event state in the second year (unless they instead experience a further CV event during that year). Different costs, different transition probabilities to other states and different utility multipliers to represent quality of life were applied to event states and post-event states.

In this model only one severity was included for each condition, therefore the model sought to represent the costs, quality of life and risk of future events of a typical 'average' patient who has experienced a certain CV event, whilst acknowledging in practice that for each condition there is a spectrum of severities, which lead to ranges of costs, quality of life and future risks.

This model did not allow transitions from PAD and heart failure to MI and stroke, although people in these states can of course experience an MI or stroke, and probabilities for these transitions are available. We have not included these transitions since people with PAD and heart failure in this model generally have worse prognoses than do people who have recently experienced MI or stroke, and so allowing such transitions out of PAD or heart failure would lead to an increase in individual life expectancy, which is unrealistic. A sensitivity analysis was performed to investigate the structural uncertainty connected with this decision.

Additional costs were added to the arms involving statin treatment to cover the costs of treating the additional cases of type 2 diabetes expected in the treatment arms. No costs were added for other adverse events. Please see Section L.2.3.7 for a full explanation.

The population of people with CVD was modelled as a single population, in line with the meta-analysis in the clinical review for this guideline which included all trials for secondary prevention, and as analysed by Ward. The NCCPC model separated the population into higher risk (acute coronary syndrome – ACS) and lower risk (CHD) groups, using effectiveness data from a small number of head-to-head trials in these populations. The complete trial evidence available for our review was analysed together in one analysis and could not be easily divided into higher and lower risk groups. People with any current or previous CV condition are at a relatively high risk of future events compared to people in primary prevention, and so the GDG considered it reasonable to model the secondary prevention population as a single group.

L.2.2.2 Primary prevention

The Markov model used to model secondary prevention was expanded to include a 'Well' health state in which all individuals start. This represents people who have never been diagnosed with any type of CVD (they may have other non-CV diseases, but these are not considered). Members of the cohort transition to a CV event health state in relation to their estimated annual risk of each event. This is made up of 2 components: baseline risk of CV events, which varies for each age and sex subgroup, and age-related risk, which increases at constant rates for both men and women (see Section L.2.3.1). Those who do not experience a first CV event or death from a non-CV cause during a cycle stay in the Well state for the next cycle.

Once a cohort member has experienced their first CV event the model continues exactly as for secondary prevention. The statin treatment option used in all arms of the model for this secondary prevention phase is assumed to be that chosen by the GDG as the recommended treatment for secondary prevention, and so the intervention given in each arm of the primary prevention model differs only whilst people are still disease-free and receiving primary prevention treatment.

The cost of treating additional cases of type 2 diabetes was included as for secondary prevention (see Section L.2.3.7). The impact of other adverse events was addressed primarily in a sensitivity analysis looking at their possible effects in making people cease taking statins or switch to a lower-intensity statin (see Section L.2.5.2).

The analysis was repeated for people with pre-existing type 2 diabetes. The same distribution of first events and the same baseline transition probabilities were used. It is not clear whether this is entirely realistic, but no data were identified which supported using different probabilities for people with type 2 diabetes. The same risk ratios were applied for statin treatment because the meta-analysis in the clinical review carried out for this guideline found no difference in effectiveness of statins for the type 2 diabetes subgroup compared to the other populations. The main difference in the model when run for the type 2 diabetes population was therefore in the use of the UKPDS risk tool rather than the QRISK2 risk tool as the basis for the different levels of risk investigated. The additional costs of treating people newly diagnosed with diabetes were not added for this population, since all patients had diabetes before the start of the model, but otherwise the model used was the same as for the general primary population.

L.2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter which was varied. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 1,000 times for the base case analyses for both the secondary prevention model and the primary prevention model and results were summarised. Subgroup analyses and sensitivity analyses were conducted deterministically (that is, based on the parameter point estimates rather than their distributions).

We checked for convergence by plotting the incremental net health benefit for high-intensity statins versus medium-intensity statins on a graph for both the secondary and primary prevention (QRISK2 CV risk score: 10%) base cases. The results had converged by the 500th iteration in both cases.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by zero and one, reflecting that a quality of life weighting will not be outside this range. Probability distributions in the analysis were parameterised using error estimates from data sources. Where this was not possible assumptions were made. The variables that were probabilistic in the model and their distributional parameters are detailed in Table 75.

Table 75: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Utility of health states	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 \times ((1-\text{mean})/\text{SE}^2) - \text{mean}$

Parameter	Type of distribution	Properties of distribution
		Beta = Alpha*×((1−mean)/mean)
Transition probabilities	Beta	Bounded between 0 and 1. As the original datasets, including number of individuals, was not available, we adopted the same procedure as the NCCPC model in assuming that SE = mean/10 and calculating beta as for utilities.
First CV events in secondary model	Joint beta distributions	Beta distributions were scaled so that the sum of all the events was 1.
Risk ratios of statin treatment	Lognormal	The natural log of the mean was calculated as follows: Mean = ln(RR) – $(SE)^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper CI) – ln(lower CI)]/1.96×2

The following variables were left deterministic (that is, were not varied in the probabilistic analysis): the cost-effectiveness threshold (which was deemed to be fixed by NICE), cost of statins (fixed), costs of health states (addressed in deterministic sensitivity analyses) and utility by age.

Deterministic sensitivity analyses were also undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

L.2.3 Model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated by clinical members of the GDG.

L.2.3.1 Baseline event rates – initial CV events

The distribution of first CV events experienced by people in the model was calculated from annual incidence rates of CV events. Incidence rates are from the same sources used by Ward and NCCPC and are taken from the Bromley Coronary Heart Disease Register[1309] (angina, MI), the Oxfordshire Community Stroke Project[140,418] (TIA, stroke), Cowie et al. 1999[359] (heart failure) and the Framingham Heart Study[991] (PAD).

L.2.3.1.1 Secondary prevention

For the secondary prevention model, fatal CV events were excluded to represent a cohort of people who had just experienced their first non-fatal CV event. The absolute incidence rates were converted into the proportions of events of each type (Table 76), summing to 100% for each age and sex subgroup. These proportions were used to allocate cohort members into a starting health state in the model.

Table 76: Relative distribution of first events in secondary prevention

	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD
Men							
40–54	20.4%	7.1%	19.6%	4.0%	8.6%	4.7%	35.6%
55–64	23.9%	5.2%	12.5%	6.5%	15.0%	9.0%	27.9%

	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD
65–74	17.0%	6.6%	13.8%	8.0%	21.5%	12.8%	20.5%
75–84	15.4%	6.5%	12.9%	6.4%	27.6%	21.0%	10.2%
85+	15.6%	7.0%	13.6%	1.2%	25.6%	28.8%	8.1%
Women							
40–54	20.3%	7.3%	5.0%	10.0%	14.3%	3.9%	39.1%
55–64	23.8%	5.0%	6.3%	6.5%	19.8%	7.3%	31.2%
65–74	15.3%	3.9%	9.2%	5.5%	29.0%	14.1%	23.0%
75–84	12.3%	2.8%	8.4%	8.1%	38.1%	20.7%	9.7%
85+	11.1%	2.4%	8.1%	7.1%	40.8%	23.8%	6.8%

L.2.3.1.2 Primary prevention – baseline risk

The same data, with the addition of fatal CV events, were also used to determine the baseline rates of first events in the primary model. The annual incidence rates for CV events were divided by the total incidence of those events which are included in the QRISK2 (Table 77) or UKPDS (Table 78) risk tools to give relative rates of each event in proportion to a nominal 100% risk score using the relevant tool. The relative rates in Table 77 and Table 78 were then multiplied by the annual CV risk to get the annual baseline risk of each event. (It is noted that the values in Table 77 and Table 78 are not meaningful before being multiplied by the annual risk, since they sum to greater than 100%.)

The annual CV risk was calculated by converting the 10-year risk (probability) into a rate and then converting this into a 1-year probability, using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where P = probability of event over time t t = time over which probability occurs (10 years)
$Transition\ probability\ (P) = 1 - e^{-rt}$	Where r = selected rate t = cycle length (1 year)

Thus, for example, a 10-year risk of 20% corresponds to a 1-year risk of 2.207%, and so for a QRISK2 risk score of 20% 10-year risk the values in Table 77 were all multiplied by 0.02207 to give the baseline transition probabilities from Well to each CV event each year.

Table 77: Relative rates of first events in primary prevention – QRISK2

	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death
Men								
40–54	0.5848	0.2038	0.5619	0.1143	0.2457	0.1359	1.0194	0.1924
55–64	0.6406	0.1387	0.3359	0.1738	0.4023	0.2424	0.7485	0.2617
65–74	0.3549	0.1376	0.2869	0.1658	0.4478	0.2662	0.4265	0.2653
75–84	0.2952	0.1252	0.2488	0.1236	0.5301	0.4035	0.1956	0.2210
85+	0.3175	0.1424	0.2760	0.0237	0.5208	0.5851	0.1654	0.2033
Women								
40–54	0.813	0.293	0.200	0.400	0.573	0.157	1.566	0.228
55–64	0.712	0.150	0.189	0.195	0.593	0.218	0.935	0.218
65–74	0.300	0.077	0.180	0.108	0.567	0.275	0.449	0.254
75–84	0.208	0.047	0.142	0.136	0.646	0.351	0.164	0.212

	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death
85+	0.182	0.039	0.134	0.116	0.670	0.390	0.112	0.197

Table 78: Relative rates of first events in primary prevention – UKPDS

	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death
Men								
40–54	0.327	0.114	0.314	0.064	0.137	0.076	0.570	0.108
55–64	0.360	0.078	0.189	0.098	0.226	0.136	0.421	0.147
65–74	0.238	0.092	0.192	0.111	0.300	0.178	0.286	0.178
75–84	0.208	0.088	0.175	0.087	0.373	0.284	0.138	0.156
85+	0.217	0.098	0.189	0.016	0.357	0.401	0.113	0.139
Women								
40–54	0.386	0.139	0.095	0.190	0.272	0.074	0.744	0.108
55–64	0.382	0.081	0.102	0.105	0.318	0.117	0.502	0.117
65–74	0.218	0.056	0.130	0.079	0.412	0.200	0.326	0.184
75–84	0.165	0.038	0.113	0.109	0.515	0.280	0.130	0.169
85+	0.149	0.032	0.110	0.095	0.549	0.320	0.092	0.161

L.2.3.1.3 Primary prevention – age-related risk

In addition, the annual risk of a first CV event increases by a fixed amount each year to account for increasing risk due to age. The magnitude of this risk was calculated in Ward 2005[1408] using a regression analysis of data from the Health Survey for England 1998. This found that the risk of any CHD event (that is, angina, MI or cardiac death) increases at a fixed absolute rate each year of 0.03% for men, 0.008% for women. Those rates have been adopted for this model, with the risk of other CV events increasing in proportion to their frequency relative to CHD.

The overall annual risk of each first event without treatment was set to be below the baseline risk in the first year, so that, as age-related risk increases, the total risk is equal to the baseline risk in the middle of the first 10-year period, and above the baseline risk by the end of the 10 year period, such that the total risk compounded over 10 years including both baseline risk and age-related risk is exactly equal to the predicted 10-year risk. Since annual risk continues to increase each year with age, it is noted that the risk in following 10-year periods will not be constant but will rise continually.

L.2.3.2 Baseline event rates – subsequent CV events

The transition probabilities between CV health states in the primary and secondary models after the first event has taken place have been taken from those identified in systematic reviews by Ward,[1408] with the addition sources identified for the NCCPC model[1003] added where necessary. The original sources of this data are the Nottingham Heart Attack Register[580,1025] (MI, strokes and CV death following CHD), the South London Stroke Register[1442] (strokes and CV death following strokes), Juul-Möller et al. 1992[729] (stable angina), Caro 2005[276] (PAD), SOLVD study[1284] (heart failure), and CURE study (unstable angina).

Ward and NCCPC did not include participants below 45 years old. This model includes people from 40 years old, and assumes the same transition probabilities for 40–44 year olds as for 45–54 year olds. Transitions from post-stable angina, post-TIA, post-heart failure and post-PAD are the same as those from the respective event states.

The sources listed above vary in age, but none are very recent. It is problematic to identify more recent baseline data as a significant proportion of the general public are now taking statins, so the baseline event figures in national registries include the effect of some people taking statins. Baseline event rates for some CV conditions have fallen in recent years – part of this is due to the effect of statins, but it is likely that there have been additional decreases due to other factors, such as the increase in revascularisation procedures. As such these transition probabilities may overestimate risk in some cases. To take account of this uncertainty, a sensitivity analysis was carried out in which the transition probabilities in this table were all reduced.

Table 79: Baseline transition probabilities

Transition from \ to	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death
Age 40–54 (men and women)								
Stable angina	0	0.0013	0.0032	0	0	0	0	0.0009
Unstable angina	0	0	0.0495	0	0.0140	0.0440	0	0.0378
Post-unstable angina	0	0	0.0186	0	0.0140	0.0440	0	0.0085
MI	0	0.0075	0.1280	0	0.0015	0.02556	0	0.0174
Post-MI	0	0.0075	0.0162	0	0.0004	0.02556	0	0.0054
TIA	0	0	0.0016	0	0.0035	0	0	0.0037
Stroke	0	0.0016	0.0016	0	0.0431	0.0037	0	0.0092
Post-stroke	0	0.0016	0.0016	0	0.0144	0.0037	0	0.0042
Heart failure	0	0	0	0	0	0	0	0.04548
PAD	0	0	0	0	0	0	0	0.08083
Age 55–64 (men and women)								
Stable angina	0	0.0029	0.0062	0	0	0	0	0.0035
Unstable angina	0	0	0.0497	0	0.0140	0.0440	0	0.0644
Post-unstable angina	0	0	0.0348	0	0.0140	0.0440	0	0.0104
MI	0	0.0075	0.1152	0	0.0032	0.02556	0	0.0333
Post-MI	0	0.0075	0.0179	0	0.0010	0.02556	0	0.0095
TIA	0	0	0.0031	0	0.0181	0	0	0.0162
Stroke	0	0.0031	0.0031	0	0.0459	0.0072	0	0.0222
Post-stroke	0	0.0031	0.0031	0	0.0186	0.0072	0	0.0098
Heart failure	0	0	0	0	0	0	0	0.04548
PAD	0	0	0	0	0	0	0	0.08083
Age 65–74 (men and women)								
Stable angina	0	0.0060	0.0110	0	0	0	0	0.0070
Unstable angina	0	0	0.0488	0	0.0140	0.0440	0	0.1077
Post-unstable	0	0	0.0632	0	0.0140	0.0440		0.0124

Transition from \ to	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	CV death
angina								
MI	0	0.0075	0.1019	0	0.0068	0.02556	0	0.0626
Post-MI	0	0.0075	0.0185	0	0.0022	0.02556	0	0.0159
TIA	0	0	0.0055	0	0.0423	0	0	0.0348
Stroke	0	0.0055	0.0055	0	0.0481	0.01278	0	0.0520
Post-stroke	0	0.0055	0.0055	0	0.0223	0.01278	0	0.0208
Heart failure	0	0	0	0	0	0	0	0.04548
PAD	0	0	0	0	0	0	0	0.08083
Age 75–84 (men and women)								
Stable angina	0	0.0091	0.0158	0	0	0	0	0.0070
Unstable angina	0	0	0.0466	0	0.0140	0.0440	0	0.1745
Post-unstable angina	0	0	0.1122	0	0.0140	0.0440	0	0.0145
MI	0	0.0075	0.0874	0	0.0141	0.02556	0	0.1136
Post-MI	0	0.0075	0.0178	0	0.0047	0.02556	0	0.0245
TIA	0	0	0.0080	0	0.0828	0	0	0.0504
Stroke	0	0.0080	0.0080	0	0.0446	0.0186	0	0.1172
Post-stroke	0	0.0080	0.0080	0	0.0246	0.0186	0	0.0412
Heart failure	0	0	0	0	0	0	0	0.04548
PAD	0	0	0	0	0	0	0	0.08083
Age 85+ (men and women)								
Stable angina	0	0.0122	0.0207	0	0	0	0	0.0070
Unstable angina	0	0	0.0425	0	0.0140	0.0440	0	0.2702
Post-unstable angina	0	0	0.1955	0	0.0140	0.0440	0	0.0167
MI	0	0.0075	0.0711	0	0.0278	0.02556	0	0.1958
Post-MI	0	0.0075	0.016	0	0.0091	0.02556	0	0.0355
TIA	0	0	0.0104	0	0.0961	0	0	0.0555
Stroke	0	0.0104	0.0104	0	0.0446	0.0242	0	0.243
Post-stroke	0	0.0104	0.0104	0	0.0252	0.0242	0	0.0375
Heart failure	0	0	0	0	0	0	0	0.04548
PAD	0	0	0	0	0	0	0	0.08083

Non-CV death is dependent on age and sex but is independent on the health state that the cohort member is currently in (see Section L.2.3.3 below).

Once the transitions to non-CV death and all transitions in Table 79 have been allocated for each cycle, all remaining individuals in an event state move to the respective post-event state, while all remaining individuals in a post-event state continue in that state.

L.2.3.3 Life expectancy and mortality rates

Life tables for England and Wales, published by the Office of National Statistics (ONS) based on 2010–2012 mortality data[1039] were used to establish population mortality rates for men and women for ages 40 to 100 years. ONS 2012 mortality statistics for England and Wales by cause of death[1038] were used to calculate the proportion of deaths for each 5-year age group which were due to circulatory (CV) or non-CV causes. These proportions were applied to the mortality rates to give the risk of death due to non-CV causes for each annual age group for both men and women.

L.2.3.4 Relative treatment effects

The risk ratios for each of the 3 statin intensity groups found in the clinical review carried out in this guideline were applied to the transition probabilities for first and subsequent CV events. The same risk ratios were used for primary and secondary prevention as the clinical review found that there was no significant difference between these subgroups – so while people with CVD have higher absolute risks of future CV events and thus higher absolute reduction in risk by taking statins compared with people at risk of CVD, the relative reduction in CV events is the same between primary and secondary prevention.

Table 80: Risk ratios (95% CIs), statin versus no treatment

Health state	Low-intensity statin	Medium-intensity statin	High-intensity statin
(Non-fatal) Stable angina	As MI	As MI	As MI
(Non-fatal) Unstable angina	As MI	As MI	As MI
(Non-fatal) MI	0.78 (0.72 to 0.84)	0.61 (0.55 to 0.68)	0.46 (037 to 0.59)
(Non-fatal) TIA	As stroke	As stroke	As stroke
(Non-fatal) Stroke	0.84 (0.75 to 0.94)	0.73 (0.66 to 0.81)	0.80 (0.70 to 0.91)
(Non-fatal) Heart failure	1	1	1
(Non-fatal) PAD	As MI	As MI	As MI
CV death	0.84 (0.78 to 0.91)	0.81	0.72
Non-CV death	0.96 (0. 90 to 1.02)	0.96 (0. 90 to 1.02)	0.96 (0.90 to 1.02)

For events which were not meta-analysed in the clinical review, the risk ratio from a related event was used (for example, the risk ratio for stroke was also applied for TIA). There is some evidence that statins cause a greater decrease in less severe events (for example, statins decrease non-fatal MIs by a larger proportion than they reduce fatal MIs), and so the GDG agreed that the decreases in these outcomes are likely to be at least this large. The efficacy of statins in treating heart failure is contested – statins may be of some benefit for less severe heart failure, but they are thought to have little or no efficacy for severe heart failure. We conservatively assume no benefit for heart failure, which is treated as a single group in this model.

The event rates reported by some of the trials included in the clinical review were for total CV events rather than first CV events, that is, more than 1 event may be counted for some participants. We have therefore needed to assume that the risk ratio of total events in the statin group compared to total events in the control group would be similar to the risk ratio of first events in statins compared to first events in the control group. The GDG agrees that this a reasonable assumption.

The risk ratios used for non-fatal stroke was taken from the clinical review investigating all (fatal and non-fatal) stroke, as this is the outcome that most clinical trials report. We are assuming that the risk ratio for non-fatal stroke will be the same as for all stroke – this may be slightly conservative, as seen by the relationship between fatal and non-fatal MI. Stroke here includes all strokes: haemorrhagic and ischaemic. Haemorrhagic strokes are increased by statins, whilst ischaemic strokes are reduced,[942] but with a net reduction in total strokes due to the greater frequency of ischaemic

strokes. Most trials only report combined strokes, so we have used the rates of combined stroke in this model.

The results of the placebo versus statin meta-analyses for stroke are inconsistent with the head-to-head meta-analysis (which showed a greater reduction in strokes with high-intensity statins), and lack plausibility, as they showed medium-intensity statins as slightly more effective than either high- or low-intensity. A sensitivity analysis was therefore undertaken to investigate this.

For non-CV death we used the results of the clinical meta-analysis for the effect of all statins as a single group versus placebo for non-CV death. The values of the meta-analysis for intensity subgroups were not significantly different from each other, or from 1.0, and did not follow a trend, so a single value was used for all intensities.

The same risk ratios fpr transitions to each CV event are applied regardless of the previous state from which the transition occurs.

It is also assumed that these risk ratios are constant regardless of baseline LDL-cholesterol levels. It is not known whether this is the case.

Hazard ratios would have been preferable to risk ratios, and these would have been used, had time-to-event individual patient-level data (IPD) been available. However, without IPD, and given the heterogeneous length of study periods in the trials encompassed in the clinical review, it was not possible to use hazard ratios.

An individual patient-level data meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration[959] suggests that statins have roughly similar effectiveness in people at different levels of CV risk, however, the number of trial participants who were at moderate to low CV risk is relatively small so this is uncertain. Effectiveness in older patients is also uncertain due to small numbers of trial participants over 80. The base case assumes equal relative effectiveness in patients at all ages and with all levels of baseline CV risk.

The trials analysed by CTT have baseline rates of CV events and death in the control groups much higher than expected event rates in a UK population, indicating that the people included in these trials may not be fully representative of the UK population, particularly in respect of primary prevention. All meta-analyses of clinical effectiveness are at risk from publication bias, but CTT required pre-registration of major trials, so there may be a lower risk of non-publication of large trials than in some other areas. Most of the trials included in our meta-analysis were undertaken with pharmaceutical industry funding, which has been found to be associated with more favourable results,[867] including in statin trials.[168]

The assumptions made in dealing with the risk ratios were tested in a number of sensitivity analyses – see Section L.2.5.3.

L.2.3.5 Utilities

We adopted the same utility multipliers for health states as Ward[1408] (these were determined following a systematic review), supplemented with values used by NCCPC[1003] for states not included in Ward's model. Though we believe these are the best available figures in each case, we acknowledge that they are sourced from multiple different studies, conducted in different settings, and which elicited quality of life preferences using different methods. As a result they may not be entirely consistent. To test these figures we included them in the probabilistic sensitivity analysis and conducted additional one-way deterministic sensitivity analyses on them.

For PAD, following stakeholder consultation, we chose not to use the value of 0.90 used by NCCPC, which was sourced from Karnon 2005,[736] which itself cited Danese 1996,[379] in which this value was

chosen on the basis of an expert assumption, but instead to use the GDG's own assumption that the impact of PAD on quality of life will on average be similar to the impact of stable angina.

Table 81: Utility multipliers of health states

Health state	Utility multiplier – mean (SE)	Source
Well	1	By definition
Stable angina	0.808 (0.038)	Melsop 2003[954]
Post-stable angina	0.808 (0.038)	Melsop 2003[954]
Unstable angina	0.770 (0.038)	Goodacre 2004,[571] Ward 2005[1408]
Post-unstable angina	0.880 (0.018)	NCCPC 2008[1003]
MI	0.760 (0.018)	Goodacre 2004,[571] Ward 2005[1408]
Post-MI	0.880 (0.018)	Tsevat 1993[1354]
TIA	0.900 (0.025)	Lavender 1998[815]
Post-TIA	0.900 (0.025)	Lavender 1998[815]
Stroke	0.628 (0.040)	Tengs 2003,[1322] Youman 2003[1470]
Post-stroke	0.628 (0.040)	Tengs 2003,[1322] Youman 2003[1470]
Heart failure	0.683 (0.020)	Davies 2006[385]
Post-heart failure	0.683 (0.020)	Davies 2006[385]
PAD	0.808 (0.038)	GDG assumption, based on stable angina
Post-PAD	0.808 (0.038)	GDG assumption, based on stable angina
CV death	0	By definition
Non-CV death	0	By definition

We also varied baseline utilities for normal health by age as adopted by Ward. Ward analysed data from Kind et al. 1998[762] and found a uniform linear regression. The utility at 40 was 0.890 and this declined with a regression of −0.00425 per year to 0.635 at 100. Age-related utilities were multiplied by health state utility multipliers.

We assumed, following Ward (which reviewed the available literature) that statin treatment does not of itself reduce utility. Adverse events may decrease utility, but they are generally of short duration, ceasing when statin treatment is discontinued, and would normally have a very small impact on annual average quality of life.

L.2.3.6 Resource use and costs

This analysis is conducted in 2014 UK pounds. All costs are assumed to remain constant (subject to discounting) at current levels throughout the length of the model. All costs exclude VAT, in line with the NICE reference case.

L.2.3.6.1 Statins

All statins are assumed to be prescribed and taken on the basis of 1 tablet per day of the specified dose (apart from fluvastatin 80 mg, for which it is assumed that 2 tablets of fluvastatin 40 mg will be taken each day).

It is noted that the prices of statins change frequently, and in particular atorvastatin has decreased in cost several times since becoming available in generic form in May 2012. Costs may continue to change in the future.

Table 82: Costs of statins

Statin	Daily dose	Cost – 28 days	Cost – annual
Fluvastatin	20 mg	£2.27	£29.61
Fluvastatin	40 mg	£2.37	£30.92
Fluvastatin	80 mg[(a)]	£4.74	£61.83
Pravastatin	10 mg	£1.16	£15.13
Pravastatin	20 mg	£1.41	£18.39
Pravastatin	40 mg	£1.77	£23.09
Simvastatin	10 mg	£0.80	£10.44
Simvastatin	20 mg	£0.86	£11.22
Simvastatin	40 mg	£1.09	£14.22
Simvastatin	80 mg[(b)]	£1.65	£21.52
Atorvastatin	10 mg	£1.03	£13.44
Atorvastatin	20 mg	£1.26	£16.44
Atorvastatin	40 mg	£1.51	£19.70
Atorvastatin	80 mg	£2.48	£32.35
Rosuvastatin (Crestor)[(c)]	5 mg	£18.03	£235.19
Rosuvastatin (Crestor)[(c)]	10 mg	£18.03	£235.19
Rosuvastatin (Crestor)[(c)]	20 mg	£26.02	£339.42
Rosuvastatin (Crestor)[(c)]	40 mg	£29.69	£387.30

Source: NHS Drug Tariff, May 2014[1021]

Fluvastatin 10 mg, pravastatin 80 mg and rosuvastatin 80 mg are not available in the UK and so are not listed.

(a) Fluvastatin 80 mg is only available in a modified release formulation (£19.20 for 28 days, £250.46 annually). The costs given here are for taking 2 fluvastatin 40 mg tablets per day, which was preferred by the GDG.

(b) The MHRA advises that, due to an increased risk of myopathy, an 80 mg dose of simvastatin should be considered only in patients with severe hypercholesterolaemia and high risk of CV complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

(c) Rosuvastatin is under patent in the UK until June 2017. The prices for all other drugs are for generic formulations.

In line with NICE policy, prescription charges are not considered in this analysis, and so it is assumed that the costs of all statins taken are borne by the NHS. However we note that in practice many of the people prescribed statins in line with the strategies investigated in this model would be under 60 and without any chronic condition or other reason for exemption from prescription charges and so, in England, would be liable to pay the prescription charge of £8.05 for each prescription (typically every 2 or 3 months).

L.2.3.6.2 Monitoring

Table 83: Monitoring resource use and costs

	During risk assessment	Usage – year 1	Usage – year 2+	Cost	Source
Appointment to take blood sample (with healthcare assistant)	1	2	1	£6.46	PSSRU 2013[365]
Appointment with nurse	1	0	0	£13.43	PSSRU 2013[365]
Appointment with GP	0	2.2	2	£45	PSSRU 2013[365]
Blood tests:					
Total cholesterol	0	2	1	£1	GDG assumption
HDL cholesterol	0	2	1	£1	GDG assumption
Triglycerides	0	0	0	£1	GDG assumption

	During risk assessment	Usage – year 1	Usage – year 2+	Cost	Source
Combined lipid profile	1	0	0	£3	GDG assumption
Liver transaminase (ALT or AST)	1	2	1	£1	GDG assumption
Creatine kinase	0.1	0	0	£2	GDG assumption
HbA_{1c}	1	1	1	£2.25	GDG assumption
Total annual monitoring costs, first year				£120.17	
Total annual monitoring costs, subsequent years				£100.71	
Annual cost of early stage type 2 diabetes (first 4 years) (4×500 mg metformin, 1×10 mg ramipril and 1×10 mg amlodipine daily, 4× GP appointments yearly, 5× Nurse appointments yearly, 1 diet management programme every 4 years)				£314.33	NHS Drug Tariff May 2014,[1021] PSSRU 2013,[369] Gillett 2010[552]

The GDG made assumptions of typical best available costs based on experience of costs from UK laboratories.

The typical numbers of tests and appointments required were discussed and agreed by the GDG. Tests carried out during the risk assessment process before statin therapy is initiated are not included in the model as they would be carried out in advance of the decision whether or not to initiate treatment, but are shown above for clarity and comparison (additionally, 1× renal function test and 1× thyroid-stimulating hormone test would be undertaken).

The GDG's recommendations in this guideline include that total and HDL cholesterol (but not triglycerides) should be checked at 3 months but not thereafter; that liver transaminase enzymes should be checked at 3 and 12 months; that creatine kinase should not be checked in asymptomatic people; and that patients should have an annual medication review. We recognise that some patients will experience adverse events whilst on statin treatment (whether related to the treatment or not) and will present to primary care to discuss these, and so we have assumed that 20% of patients will have an additional appointment to cover this. Given the increased risk of developing type 2 diabetes whilst receiving statin treatment, we have assumed 1 annual HbA_{1c} test.

In addition, though not recommended by the GDG, we have conservatively assumed that patients will on average use some additional resources. We have assumed that total and HDL cholesterol will be measured annually, and that each patient will have 1 additional consultation in the first year, initiated either by the patient or a clinician. We have conservatively assumed that all consultations will be face-to-face surgery appointments with a GP (£45), rather than telephone consultations with a GP (£27) or face-to-face appointments with a specialist nurse (£25) or nurse (£13.43).[369] We note that the cost of an annual supply of most statins is below £20 (£36 for atorvastatin 80 mg), and so the cost of GP consultations is considerably higher than the cost of the statins themselves, for all generic statins.

Two appointments will also be required in the first year (at 3 and 12 months) to take blood samples for the tests recommended by the GDG, with 1 annual appointment thereafter. These may be with a healthcare assistant, phlebotomist or pharmacist. We have used the costs presented by PSSRU for a nursing clinical support worker.[369]

L.2.3.6.3 Health states

Table 84: Costs of health states

Health state	Cost in state [(a)]
Well	£0
Stable angina	£7736
Post-stable angina	£240

Health state	Cost in state [(a)]
Unstable angina	£3313
Post-unstable angina	£385
MI	£3337
Post-MI	£788
TIA	£578
Post-TIA	£124
Stroke	£4092
Post-stroke	£155
Heart failure	£2297
Post-heart failure	£2597
PAD	£952
Post-PAD	£529
CV death	£1174
Non-CV death	£0

(a) Cost of first 6 months for event states, 1 year for post-event states

Costs of health states were based on estimates of resource use that a typical adult with that CV condition would be expected to receive in line with NICE guidance and standard NHS practice. Costs were sourced from the NHS Drug Tariff, May 2014,[1021] NHS Reference costs 2012–13,[422] PSSRU Unit Costs of Health & Social Care 2013[369] and BNF, May 2014.[717] Standard dosages were taken from BNF, May 2014.[717]

L.2.3.7 Adverse events

People taking statins may experience adverse events, which, as with all drugs, may be caused by the drugs themselves or may be coincidental. The rates of adverse events experienced by people taking statins are however uncertain and highly controversial.

One reason for this uncertainty is that the reporting of adverse events is not consistent amongst statin trials, with different studies reporting different adverse events, and appearing to differ in the definitions used for those events which they do report, leading to very large disparities in the total rates of adverse events reported by different studies. However, most trials show rates of adverse events which are very similar between control and treatment arms.

A recent review by Finegold et al. (2014){FINEGOLD2014} of 29 statin RCTs found statins to be associated with a significant increase in adverse events only for diabetes and raised liver transaminases. It found no evidence of other adverse effects being attributable to statin use, and no difference in rates of withdrawal from treatment between statin and control groups. Reviews by the CTT Collaboration{ANON2010A} and The Cochrane Collaboration{TAYLOR2013} agree on the general safety of statins and the lack of difference in rates of most adverse events between treatment and control groups in published trials.

We also studied a review by Naci et al. (2013).{NACI2013} This conducted a network meta-analysis on the adverse events of statins, using study-level data from 135 RCTs representing 246,955 participants, and compared rates of events between each dose of each statin used where data were available. We considered this to be the most comprehensive and highest quality study of adverse events. The review found that statins as a class were associated with higher rates of diabetes diagnosis and raised liver transaminases, but were no different from control in rates of myalgia, raised creatine kinase, cancer and discontinuation of treatment due to adverse events. When individual statins and individual doses were investigated further differences between statins were noted.

The second reason for the uncertainty surrounding the true rates of adverse events with statins is the discrepancy that many clinicians, particularly those working in primary care, observe between the reported rates of adverse events in clinical trials and those that they experience when seeing patients taking statins routinely. Some adverse events are in any case common in people of the age and health profile likely to be prescribed statins, and so the problem with observations such as these is the lack of a control population. However, there is also a concern that the protocols followed by many of the major statin trials were such that they artificially reduced the rate of adverse events in those trials. Trials often also excluded those with some comorbidities and older people. Some trials had introductory run-in phases in advance of the start of the trial, in which patients unable to tolerate the drug or who wished not to continue could drop-out before the trial started. We accept that this may account for some of the discrepancy between the rates of adverse events reported in trials and those anecdotally reported in routine primary care. However we also note that the major effect of this approach in trials is that people who were unable to tolerate statins dropped out soon after initiating treatment. In the recommendations in this guideline we advise those people experiencing adverse events to first test whether the adverse event is connected with their treatment by suspending and restarting treatment, and then to reduce the dose or intensity of their statin treatment, or to cease treatment if they cannot or do not wish to find a statin dose which they can tolerate. In practice the effective will be similar to the clinical trials in that only those people who can tolerate a statin well will continue with it for the medium or long term. To account for this we have modelled the impact if a significant proportion of people initiating statin treatment were to change or withdraw from treatment. This is discussed further below and in Section L.2.5.2.

Observational research conducted by Hippisley-Cox et al. (2010) has analysed routinely collected general practice data to compare rates of adverse events in those people taking or not taking statins.{HIPPISLEYCOX2010A; HIPPISLEYCOX2010} This found evidence supporting increased risks of liver dysfunction, acute renal failure, myopathy and cataract. We make a research recommendation (see Appendix N.5) for new research to be conducted in routine primary care on the relative rates of adverse events in different doses of statins.

To model the impact of adverse events on the cost effectiveness of statin treatment we have added extra costs and disutilities to the model to cover the effect of treating those people diagnosed with diabetes as a result of statin treatment. This is a new addition to previous models of statin treatment. We have also conducted analyses examining the impact of high rates of patients withdrawing from treatment or switching from one statin to another in response to adverse events.

L.2.3.7.1 Type 2 diabetes

The clinical review for this guideline found that statins increase the diagnosis of type 2 diabetes by an average of 9% (risk ratio: 1.09, 95% CI 1.03 to 1.17) in trials lasting 2–5 years, an increase in the crude incidence rate of from 4.3% to 4.7%. This finding was supported by a meta-analysis by Sattar et al. (2010){SATTAR2010A} which reported an odds ratio (OR) of 1.09 (95% CI 1.02 to 1.17) and the network meta-analysis by Naci et al.{NACI2013} with an OR also of 1.09 (95% CrI 1.02 to 1.16). Finegold{FINEGOLD2014} found statins to be associated with an increase from an absolute risk of developing diabetes from 2.4% to 3% in primary and secondary prevention combined, with an increase in primary prevention of 0.5% (95% CI: 0.1% to 1.0%) from 2.2% to 2.7%.

The association between statins and new cases of diabetes is now well established, and as such constitutes the most clear adverse effect of statin treatment. However, it is less clear what the increase in cases of diabetes being diagnosed represents. In the base case we have assumed that these additional diagnoses in fact represent cases of diabetes being brought forward in people who would otherwise still have been expected to contract diabetes later in life.

The review in this guideline of the evidence for factors affecting the prediction of adverse events with statin therapy identified a high frequency of components of the metabolic syndrome (insulin resistance syndrome) as the best predictor of new cases of diabetes in patients receiving statin

therapy. Trials of lifestyle and pharmacological intervention have been performed in people with components of the metabolic syndrome using onset of newly diagnosed diabetes as an end point. The baseline rate for change in HbA_{1c} was approximately 0.075% per year in the 'placebo' or minimal intervention group in the Diabetes Prevention Program (DPP) trial.[772] Statins raised HbA_{1c} by 0.3% in clinical trials so it was calculated that this would translate into the diagnosis of type 2 diabetes being brought forward by an average 4 years.

We assumed that with no treatment 5% of individuals without CVD would be diagnosed with type 2 diabetes during the primary prevention phase, and 10% of individuals with CVD would be diagnosed with type 2 diabetes during their time in secondary prevention. The risk ratios for low-, medium- and high-intensity statins in our clinical review were 1.05, 1.11 and 1.25 respectively and so these were used to calculate the proportion of the individuals who were due to develop diabetes who would be diagnosed earlier if treated with each intensity of statin.

The costs of the first 4 years of diabetes treatment for these people were added to all statin arms of the model compared with no treatment. Whilst this onset will obviously occur at different times for different people, it is assumed (conservatively, in relation to discounting) that this happens early on average, and so the additional costs are added to years 3, 4, 5 and 6 of treatment.

The clinical review conducted for this guideline included only 1 RCT[107] in the high-intensity arm, from which the risk ratio of 1.25 was calculated. However, a recent meta-analysis by Preiss et al. (2011)[1109] has meta-analysed the results of those head-to-head statin trials which reported new-onset diabetes to compare the rates in higher- and lower-intensity statins groups. This found a risk ratio of 1.12 (12% increased risk) for higher-intensity statins compared to the lower intensity arms of these trials. Combining a risk ratio (RR) of 1.12 with the RR of 1.11 for medium-intensity versus no treatment in our clinical review gives a RR of 1.24, very close to the value of 1.25 used.

As it is not clear whether all of the excess cases of diabetes seen with statin treatment are necessary only cases which have been brought forward, we also conducted additional sensitivity analyses to explore the impact if 25% or, to use the most extreme scenario, 100% of the additional diagnoses represent entirely additional cases of diabetes that would not otherwise have occurred. See Section L.2.5.3.8 for further details.

L.2.3.7.2 Myalgia and myopathy

Myalgia (that is, some degree of muscle pain, soreness or weakness) and myopathy (muscle pain along with raised creatine kinase levels, indicating biochemical evidence of muscle damage) are the adverse events most commonly discussed in association with statin use. Myalgia is also common in the general population. As such it is hard to tell which cases of myalgia are related to statin use, although the response may be the same in either case: to advise reducing the dose or intensive of statins or to cease taking statins. The review by Naci{NACI2013} found no significant difference in reported rates of myalgia between any statin and control, and a significantly different rate of raised creatine kinase levels only for simvastatin 80 mg, for which the MHRA has already warned of risk of myopathy. The observational study by Hippisley-Cox{HIPPISLEYCOX2010A} did find an increase in moderate to serious myopathy (including rhabdomyolysis), although this was not a controlled trial, and so the magnitude of these.

We meta-analysed the reported rates of myalgia in the trials included in our clinical review (see Section 11.3.1 for evidence profiles and Appendix I.4 for forest plots). We note that different studies used (explicitly or implicitly) different definitions of myalgia, and so the absolute rates of myalgia in control and treatment arms vary greatly between trials. In comparing treatment with control we found no evidence of difference, either for statins as a whole or for any intensity or population group. However we did find evidence for a higher rate of myalgia in the head-to-head comparison of high-intensity and medium-intensity statins (RR 1.86, 95% CI: 1.35 to 2.57); this was based on results from 2 trials.

In this guideline we recommend that patients taking statins are monitored for side effects, including a primary care consultation within the first 3 months of starting treatment. People given statins should also be advised to consult their GP if they experience any symptoms that they believe may be connected with starting statin treatment. Where muscle pain is related to statin use, this normally appears soon after starting treatment. We have therefore assumed that most muscle-related adverse events (whether caused by statins or coincidental) will be reported to a doctor soon after starting treatment, and statin treatment will be varied or stopped as a result. Consequently we account for the impact of any excess myalgia that may be caused by statins by the scenario analysis in Section L.2.5.2. As we expect that people will stop taking the statin which may have been affecting them, we do not expect there to be any long-term health effects for these people.

L.2.3.7.3 Rhabdomyolysis

Rhabdomyolysis is a more severe form of muscle adverse event, where muscle tissue breaks down. It is more serious than myalgia or myopathy, and if not quickly prevented can lead to lasting impacts on health, including death.

Rhabdomyolysis is subject to different definitions and severities. For the clinical review we adopted the definition of levels of creatine kinase more than 10 times the upper limit of normal, although the most severe effects of rhabdomyolysis would only be expected with creatine kinase levels considerably higher than these. We found no significant difference between statin and control for any intensity or population, with a small but not significant increase for statins as a whole (RR: 1.21, 95% CI: 0.69 to 2.12), representing an increase from 18 cases in 37,681 control participants (0.05%) to 24 cases in 38,147 statin participants (0.06%).

Our head-to-head review of high-intensity statins compared with low-intensity statins showed an increased risk for high-intensity statins, although this result was dominated by 1 study{RAGGI2005} which reported a rate of rhabdomyolysis of over 3% in the high-intensity group, a rate so out of line with all the other trials that the definition of rhabdomyolysis used in this study must be questioned. Our head-to-head review of high-intensity statins compared with medium-intensity statins showed an increased risk for high-intensity statins of 0.3% compared to 0.07% (RR: 4.15, 95% CI: 2.27 to 7.59). All studies included in this review used as their high-intensity statin simvastatin 80 mg, which is known to give rise to higher rates of muscle adverse events, and is subject to a warning from the MHRA. None of these studies looked at atorvastatin.

The network meta-analysis by Naci{NACI2013} found limited information on rhabdomyolysis compared to other adverse events, with no evidence than any statin examined differed from control or each other. In a 2006 safety review,{LAW2006} Law and Rudnicka suggest a rate of rhabdomyolysis of around 1 per 100,000 person-years with fluvastatin or pravastatin and around 4 per 100,000 person-years with simvastatin or atorvastatin, based on trials and safety notification data, rates many times lower than those associated with cerivastatin, which was withdrawn due to the high rates of adverse effects.

In summary, the available evidence gives no clear answer as to whether there is an increased risk of rhabdomyolysis with those statins currently available, but any risk that there may be would be very small in terms of frequency of cases.

Although a proportion of these cases may lead to serious health impacts, the very low rate of cases mean that whatever costs and disutilities were applied to people who experience rhabdomyolysis could not make an appreciable impact on the total costs and quality of life per person in the model, and consequently we have not included calculations for rhabdomyolysis in this model.

L.2.3.7.4 Liver adverse events

Effects of statins on the liver are assessed by monitoring liver transaminase levels. Levels greater than 3 times the upper limit of normal are considered a cause for concern, although doctors will

need to interpret the significance of this result for individual patients based on their history, lifestyle and other risk factors.

Our clinical review showed an increase in the proportion of people with raised transaminase levels with statins (RR 1.90, 95% CI: 1.56, 2.32), although the absolute rates were low: 0.35% for control and 0.66% with statins. It also showed increases for high-intensity statins compared with low- or medium-intensity statins.

These results were in line with other research. The observational study Hippisley-Cox{HIPPISLEYCOX2010A} showed increases for all statins (RRs of between 1.21 and 2.53) with these being statistically significant in most cases. The network meta-analysis by Naci{NACI2013} showed significant increases in the proportion of people with raised transaminases for atorvastatin 40 mg and 80 mg, fluvastatin 40 mg and simvastatin 80 mg. The review by Finegold{FINEGOLD2014} found that the proportion of people with raised liver transaminases was an additional 0.4% (95% CI: 0.2% to 0.6%) of primary prevention patients and 0.4% (95% CI: 0.2% to 0.7%) of secondary prevention patients.

Raised transaminase levels alone do not require additional treatments. In line with our recommendations for monitoring people taking statins, we assume that those found to have raised transaminase levels will have their statin treatment modified or stopped as appropriate, and so they will not experience any lasting negative health effects. People with raised transaminases are hence included in our adverse events scenario analysis in Section L.2.5.2, but no further changes to costs or quality of life have been made to the model in respect of these events.

L.2.3.7.5 Other adverse events

An individual patient meta-analysis by the CTT Collaboration{EMBERSON2012} of 174,149 participants has shown that statins have no effect on cancer, either in trials of statin versus control (incidence RR: 1.00, mortality RR: 1.00) or in head-to-head trials of higher-intensity versus lower-intensity statins (incidence RR: 1.00, mortality RR: 0.93, 95% CI 0.82 to 1.06). This is supported by the observational study by Hippisley-Cox{HIPPISLEYCOX2010A} which found no association between statins and melanoma or gastric, lung, renal, breast or prostate cancer, and a slight reduction in oesophageal cancer, which was significant for some but not other statins.

Hippisley-Cox also found no association between statins and Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia or osteoporotic fracture.

This study did find an association between statin use and increased risk of acute renal failure in men and women taking atorvastatin, pravastatin or simvastatin and women taking fluvastatin (RRs of between 1.50 and 2.19) with insufficient data on rosuvastatin. However, with a crude incidence of 1.80 cases per 10,000 person-years in women and 2.45 per 10,000 person-years in men the effect of this increase would be very small. Including costs and quality of life connected to this event to the model could not make a significant effect on the results of the model. Given the uncertainty with regard to whether there is a connection between renal failure and statins, and the very small number of people who would be affected if such a relationship were to be the case, we have not included renal failure in the model.

Hippisley-Cox found an association between statins and a slightly increased risk of cataract (RRs between 1.16 and 1.56 depending on the statin). Due to the lack of data on this adverse event from other studies, particularly RCTs, the GDG did not feel it was appropriate to model this event.

L.2.3.7.6 Discontinuation due to adverse events

Adverse events connected with statin use are widely assumed to be related to withdrawal from statin treatment and the decline in adherence with treatment over time,{ZHANG2013} although a similar pattern of falling continuance is found with other long-term cardiovascular

medication.{CHOWDHURY2013} The network meta-analysis by Naci{NACI2013} found no evidence for differential discontinuance due to adverse events in for statins as a whole or individual statins compared with control. However, when individual doses were compared there was an increased rate of discontinuation in people taking atorvastatin 40 mg (OR: 2.72) or 80 mg (OR: 1.69) or fluvastatin 20 mg (OR: 2.26). Finegold{FINEGOLD2014} found the rates of discontinuation in 10 primary prevention trials to be 12.1% of statin patients and 13.4% of control patients, and the rates in 9 secondary prevention trials to be 12.9% of statin patients and 15.2% of control patients.

Despite limited evidential support for increased rates of discontinuation due to adverse events in people taking statins, we are aware of a widespread concern that this may be the case. We also note the small increases found in the rates of raised liver transaminases, and of myalgia with high-intensity statins, which may be expected to lead to increased discontinuance if patients do not successfully switch onto an alternative dose of statin. Therefore we have conducted additional scenario analyses to consider the impact if high-intensity statins do lead to an increase rate of switching and discontinuation compared with lower intensities of statins (see Section L.2.5.2). In addition, the effect of a high rate of discontinuance in all statin groups, regardless of cause, is explored further by the sensitivity analysis outlined in Section **Error! Reference source not found.**.

L.2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross-referencing age as a respective risk factor for mortality. Baseline utility was also time dependent and was conditional on the age of the participants.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the CV death and non-CV death transition probabilities.

Quality-adjusted life years for the cohort were computed for each annual cycle by multiplying the number of individuals in each health state at the start of the year by the utility multiplier for that health state and multiplying by 0.5 for the first half of the year, to reflect the assumption that all events take place halfway through each cycle; and repeating for the health states at the end of the year to account for the quality of life during the second half of the year. All combined annual values were multiplied by the baseline utility for the age of the cohort members during that cycle. QALYs were then discounted to reflect time preference (discount rate = 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle were summed in the same way as QALYs. A half-cycle correction was applied to costs: it was assumed that CV events which occur in any annual cycle on average take place halfway through the year. The costs given for 'event' states cover the first 6 months after the event. It is assumed that the costs for the following 6 months are the same as half the annual cost of the respective 'post-event' state. Higher monitoring and appointment costs were applied to all individuals undergoing treatment in their first year of both primary and secondary treatment. Lower costs were applied to all subsequent years. It was conservatively assumed that people dying during a year would incur a full year's worth of statins and monitoring appointments. The costs incurred by bringing forward the diagnosis of type 2 diabetes in a proportion of patients by 4 years were added in cycles 3, 4, 5 and 6. Costs were discounted to reflect time preference (discount rate: 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

L.2.5 Sensitivity analyses

L.2.5.1 Threshold analysis – effectiveness of different doses within the same intensity class

It was not possible to obtain sufficient data to compare the clinical effectiveness of all 18 doses of statins. They were hence combined into 3 groups (low, medium and high intensity). The base case analyses thus assume that all statin doses within each group have equal effectiveness and equal likelihood of giving rise of adverse events; the only factor which is varied between statin doses within the same class is the cost of the drug. Hence within each class the cheapest drug will appear the most cost effective.

However, it is known that the different statin doses do differ with respect to their ability to reduce total cholesterol and LDL cholesterol – surrogate measures of effectiveness. It is believed that there is also a difference in the ability of different statin doses to reduce CV events, but the size of this difference is not clear, which is why we are unable to include it in the model base case.

Instead, a threshold analysis was carried out to compare 2 or more statin doses in the most effective intensity class which appeared to be cost effective. This increased the risk ratios for the higher-dose statin by increments of 1% relative to the risk ratios for the lower-dose statin to assess whether at these potential levels of clinical effectiveness the higher-dose statin would be cost effective compared to the cheapest treatment within the class. The risk ratios for heart failure and non-CV death were not changed.

L.2.5.2 Adverse events scenario analysis

As discussed in Section L.2.3.7 above, the GDG is aware of concern that high-intensity statins may give rise to a higher rate of adverse events than lower-intensity statins, leading patients to cease taking statins or to switch to a different statin to avoid these adverse events. We therefore investigated whether higher rates of discontinuation and switching in people taking high-intensity statins compared to medium-intensity would affect the cost effectiveness of high-intensity statins.

In the first analysis we assumed that of those who initiated primary prevention treatment with high-intensity statins,

- 5% would cease taking any statins
- 5% would change to taking medium-intensity statins
- 90% would continue taking high-intensity statins.

Of those who initiated treatment with medium-intensity statins

- 2% would cease taking any statins
- 2% would change to taking low-intensity statins
- 96% would continue taking high-intensity statins.

These rates of change of treatment are much higher than the rates of adverse events seen in clinical trials, but are conservative in light of anecdotal reports of much higher rates of adverse events in routine clinical practice. For low-intensity treatment it was assumed that 100% of individuals would continue taking the therapy. No changes were made to statin usage in the later secondary prevention stage of the primary prevention model.

All those stopping or switching would incur additional consultation and monitoring costs (1 GP appointment, 1 healthcare assistant appointment, 1× total cholesterol, HDL cholesterol, liver transaminase, creatine kinase and HbA_{1c} tests).

In the second analysis the scenario was repeated, but with higher rates of changing treatment. Of those who initiated treatment with high-intensity statins

- 10% would cease taking any statins
- 10% would change to taking medium-intensity statins
- 80% would continue taking high-intensity statins.

Of those who initiated treatment with medium-intensity statins

- 5% would cease taking any statins
- 5% would change to taking low-intensity statins
- 90 would continue taking high-intensity statins.

L.2.5.3 One-way deterministic sensitivity analyses

One-way sensitivity analyses were conducted by varying the following parameters.

L.2.5.3.1 Costs

- The costs of all health states: –50%, +100%.
- The cost of monitoring appointments: conducted by nurses not GPs.

L.2.5.3.2 Utilities

- Utility multipliers for health states (lower CIs, upper CIs; calculated from mean and SE).
- Age-related utility decrement: removed, all ages = 1.0.

L.2.5.3.3 Discounting

- Discount rate: 1.5% for both costs and benefits.

L.2.5.3.4 Baseline CV event rates transition probabilities

- All transition probabilities in Table 79 (which does not include non-CV death) multiplied by 0.9 (90%) to represent a possible decrease in CV events in the UK population since the studies from which the base case figures were taken.
- All transition probabilities in Table 79 multiplied by 0.8 (80%).

L.2.5.3.5 Risk ratios

- RR1: the upper confidence intervals (that is, those closest to 1.0) used for all risk ratios.
- RR2: the lower confidence intervals used for all risk ratios.
- RR3: risk ratio of 0.78 used for all intensity classes for stroke and TIA instead of varying by intensity.
- RR4: the risk ratios for high-intensity statin versus no treatment were calculated by multiplying the risk ratios for medium-intensity statin versus no treatment by the risk ratios for the high versus medium head-to-head trial meta-analysis; with stroke and TIA held constant at 0.78 for all intensities
- RR5: as RR4, but with stroke and TIA also calculated the same way
- RR6: non-CV death varied by intensity group using the results of the meta-analysis (low: 0.98, medium: 0.93, high: 1.00)
- RR7: the medium versus low and high versus low results of a recent network meta-analysis by Ribeiro et al. 2013),[1141] which looked at the same intensity groups and a similar group of trials, were applied to our low versus no treatment risk ratios to generate new risk ratios for medium and high versus no treatment

L.2.5.3.6 Duration of effect

- 20 years

- 10 years
- 5 years
- 1 year

Treatment was given for 1, 5, 10 or 20 years instead of for the whole lifetime, after which time treatment is assumed to cease, but with the costs and benefits assessed over the whole lifetime. It was assumed that the clinical benefits of statin treatment ceased immediately when treatment ended and CV risk returned to that for the no treatment group; this was a conservative assumption. (For the primary prevention model, this analysis assessed the implications if primary prevention treatment was effective for only a limited time; treatment in the secondary phase – which is the same in all arms of the primary model – was still assumed to have life-long efficacy).

L.2.5.3.7 Continuance with treatment

- The impact on cost effectiveness if 50% patients cease taking statins after 1 year, after incurring full drug and monitoring costs for the first year. with the remaining 50% continuing treatment until death.

L.2.5.3.8 Type 2 diabetes

In the base case it was assumed that all additional cases of type 2 diabetes seen with statin treatment are expected cases of diabetes being brought forward for 4 years. In this analysis we assessed the impact if in fact

- 25%, or
- 100%

of cases were in fact additional cases of diabetes that would not have occurred without the use of statins. In this case costs were added for standard diabetes medication and appointments and the costs of dealing with complications of diabetes, and utility decrements were added to account for the effect of complications of diabetes.

The standard costs used were £314 per year for first 4 years, as in Table 83 above; £312 for the next 5 years (sulfonylurea added but no diet management programme); £1333 for subsequent years (as for the second stage with the further addition of insulin). The complications included were leg or foot amputation, chronic kidney disease including renal replacement treatment, and retinopathy. The prevalence of complications were taken from the National Diabetes Audit 2011–12[624] and costs from NHS Reference costs 2012–13.[422]

It was conservatively assumed that amputations would give rise to a total (lifetime) disutility of −5 QALYs and retinopathy requiring treatment would be associated with a disutility of −1 QALY per treatment episode. A disutility of −0.271 QALYs was added for each year of renal replacement treatment, based on a study by Kiberd and Jindal (1995).{KIBERD1995}

L.2.5.3.9 Structural uncertainty

- Allowing transitions out of the heart failure and PAD event and post-event states (not allowed in the base case).

L.2.5.4 Cost-effectiveness threshold

- The effect of varying the cost-effectiveness threshold from £20,000 per QALY gained to £30,000 per QALY gained was assessed by comparing the QRISK2 risk scores at which different statin doses become cost effective for each age and sex subgroup.

L.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that plausible results were generated for given inputs. The model was peer reviewed at an interim stage by an external health economist; this included systematic checking of the model calculations. Minor comments made were incorporated into the model.

L.2.7 Estimation of cost effectiveness

The most widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If the costs of one intervention are lower than those of a second, and the QALYs gained from that intervention are higher than from the other, then the first option is said to dominate the second and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net health benefit (NHB). This is calculated according to the formula below. The decision rule then applied is that the comparator with the highest NHB is the cost effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Health\ Benefit\ (X) = \left(QALYs(X)\right) - Costs(X) / \lambda$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation and presentation of the results NHB is used in all analyses in this report to identify the optimal strategy, with ICERs also reported for some analyses where helpful.

Results are also presented graphically for the probabilistic results for the base case analyses. Comparisons not ruled out by dominance or extended dominance are joined by lines on the graph where the slope represents the incremental cost-effectiveness ratio between 2 options.

L.2.8 Interpreting results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[991] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominates other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per QALY gained compared with the next best strategy.

L.3 Results

L.3.1 Secondary prevention of CVD

L.3.1.1 Comparison of all 19 options

Analysis at base case: men, age 60 at start of model. Deterministic results are shown in Table 85.

Table 85: Comparative cost effectiveness of all secondary treatment options

Class	Drug	Cost (lifetime cost per person)	QALYs (lifetime QALYs per person)	Net health benefit [(a)]
No treatment	None	£9,501	6.862	6.387
Low intensity	**Simvastatin 10 mg**	**£11,229**	**7.230**	**6.669**
Low intensity	Pravastatin 10 mg	£11,288	7.230	6.666
Low intensity	Pravastatin 20 mg	£11,328	7.230	6.664
Low intensity	Pravastatin 40 mg	£11,387	7.230	6.661
Low intensity	Fluvastatin 20 mg	£11,468	7.230	6.657
Low intensity	Fluvastatin 40 mg	£11,484	7.230	6.656
Medium intensity	**Simvastatin 20 mg**	**£11,155**	**7.307**	**6.749**
Medium intensity	Atorvastatin 10 mg	£11,183	7.307	6.748
Medium intensity	Simvastatin 40 mg	£11,192	7.307	6.747
Medium intensity	Fluvastatin 80 mg	£11,791	7.307	6.717
Medium intensity	Rosuvastatin 5 mg	£13,972	7.307	6.608
High intensity	**Atorvastatin 20 mg**	**£11,403**	**7.480**	**6.910**
High intensity	Atorvastatin 40 mg	£11,445	7.480	6.908
High intensity	Simvastatin 80 mg	£11,469	7.480	6.907
High intensity	Atorvastatin 80 mg	£11,608	7.480	6.900
High intensity	Rosuvastatin 10 mg	£14,223	7.480	6.769
High intensity	Rosuvastatin 20 mg	£15,567	7.480	6.702
High intensity	Rosuvastatin 40 mg	£16,184	7.480	6.671

(a) At a cost-effectiveness threshold of £20,000 per QALY gained

This analysis assumes equal clinical effectiveness of all drugs in the same class and no difference in adverse events. As a result the cheapest drug in each intensity class is cost effective compared to all other drugs in that class.

L.3.1.2 Comparative cost effectiveness of the cheapest option in each intensity class

Analysis at base case: men, age 60 at start of model. Results are shown in Table 86.

Table 86: Comparative cost effectiveness of secondary treatment, base case (deterministic)

Class	Drug	Cost	QALYs	Net health benefit	Comparison	Incr cost	Incr QALYs	ICER (per QALY gained)	Rank of net benefit
None	None	£9,501	6.862	6.387					4
Low	S10	£11,229	7.230	6.669	Low – NT	£1,729	0.368	£4,697	3
Med	S20	£11,155	7.307	6.749	Med – Low	−£75	0.077	Dominates	2
					Med – NT	£1,654	0.445	£3,716	
High	A20	£11,403	7.480	**6.910**	High – Med	£249	0.173	£1,436	1
					High – NT	£1,903	0.618	£3,078	

This analysis was repeated using probabilistic methods, as outlined in Section L.2.2.3. The results are shown in Table 87 and Figure 166.

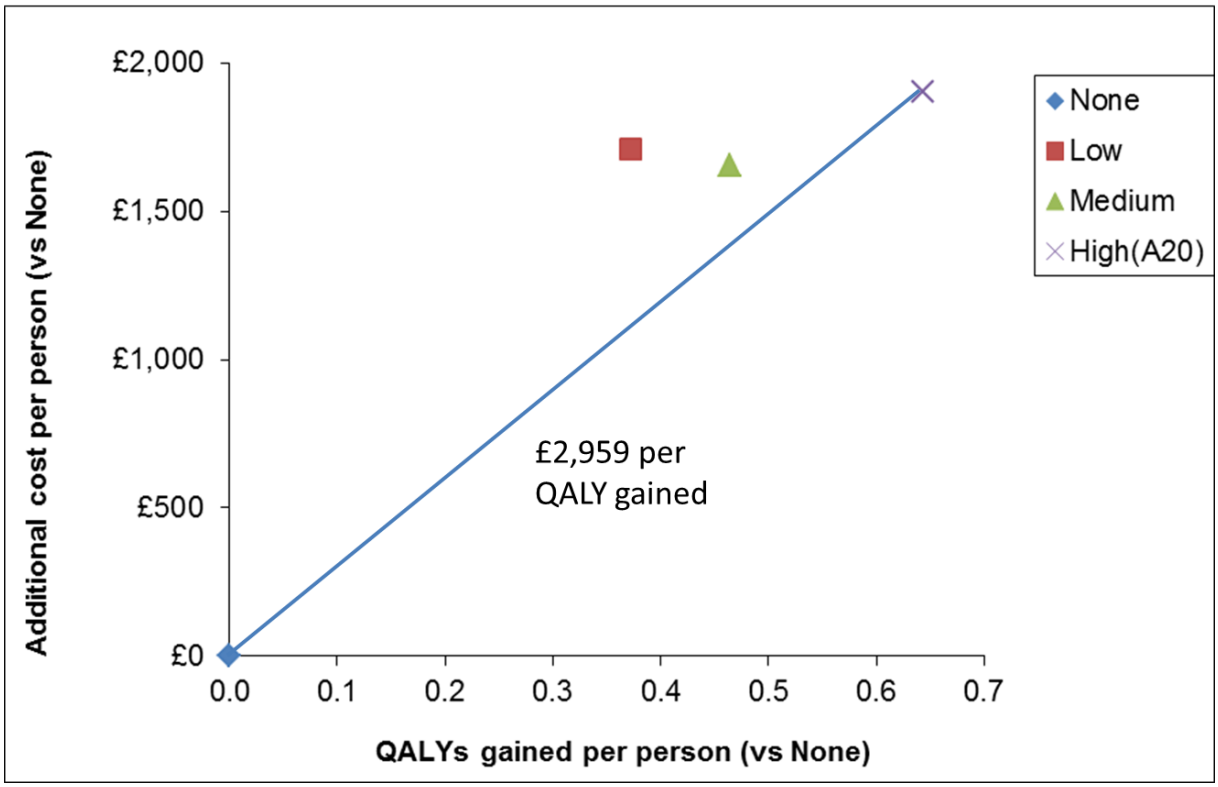
Table 87: Comparative cost effectiveness of secondary treatment, base case (probabilistic)

Class	Drug	Cost	QALYs	Net health benefit	Comparison	Incr cost	Incr QALYs	ICER (per QALY gained)	Rank of net benefit (95% CI)
None	None	£9,404	6.764	6.293					4 (4 to 4)
Low	S10	£11,116	7.135	6.579	Low – NT	£1,712	0.372	£4,605	3 (1 to 3)
Med	S20	£11,057	7.228	6.675	Med – Low	−£58	0.093	Dominates	2 (1 to 3)
					Med – NT	£1,653	0.465	£3,559	
High	A20	£11,307	7.407	**6.841**	High – Med	£249	0.179	£1,397	1 (1 to 3)
					High – NT	£1,903	0.643	£2,959	

High-intensity statin treatment was cost effective in 86.6% of 1000 simulations, medium intensity in 11.7%, low intensity in 1.7% and no treatment in 0%.

Medium-intensity statins are cost effective compared to no treatment and dominate low-intensity statins (that is, they are both cheaper and more effective). High-intensity statins (atorvastatin 20 mg) extendedly dominate both medium- and low-intensity statins and are cost effective compared to no treatment with an ICER of £2959 per QALY gained (deterministic: £3078) and the highest net health benefit (NHB) of 6.841 (6.910). The deterministic results from the model are almost identical to the probabilistic results. The subgroup analyses below use deterministic results only.

Figure 166: Cost effectiveness of statins for secondary prevention (probabilistic)



If atorvastatin 40 mg or 80 mg are chosen as the comparator from the high-intensity group instead of atorvastatin 20 mg, then high-intensity treatment still extendedly dominates medium-intensity treatment since the ICERs for these comparisons are below that for medium-intensity treatment versus no treatment (£3716 per QALY gained). See Table 88 and Table 89 below.

Table 88: Comparative cost effectiveness of secondary treatment, high intensity (atorvastatin 40 mg) versus medium intensity (simvastatin 20 mg)

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
Med	S20	£11,155	7.307	6.749			
High	A40	£11,445	7.480	**6.908**	£291	0.173	£1,679

Table 89: Comparative cost effectiveness of secondary treatment, high intensity (atorvastatin 80 mg) versus medium intensity (simvastatin 20 mg)

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
Med	S20	£11,155	7.307	6.749			
High	A80	£11,608	7.480	**6.900**	£454	0.173	£2,621

L.3.1.3 Threshold analysis – effectiveness of different doses of atorvastatin

Atorvastatin 20 mg, 40 mg and 80 mg are all drugs within the high intensity class. Therefore they were modelled in the base case analysis with equal effectiveness because the meta-analysis in the clinical review looked at the effectiveness of all drugs in this class together. (Sufficient trials of atorvastatin 20 mg and 40 mg do not exist to be able to compare them with atorvastatin 80 mg directly in terms of CV event outcomes.)

The only factor which was varied in the model between these doses of atorvastatin in the base case analysis is the cost of the drug. As a result, the cheapest drug (atorvastatin 20 mg) has been found to be most cost effective.

However, it is known that atorvastatin 20 mg, 40 mg and 80 mg do differ with respect to their ability to reduce total cholesterol and LDL cholesterol – surrogate measures of efficacy (atorvastatin 20 mg has been associated with a reduction in LDL cholesterol of 43%, atorvastatin 40 mg with a reduction of 49% and atorvastatin 80 mg with a reduction of 55%[808]). It is believed that there is also a difference in their ability to reduce CV events, but the size of this difference is not known.

This threshold analysis looks at how much greater the effectiveness of atorvastatin 40 mg or 80 mg would have to be to make them cost effective compared to atorvastatin 20 mg. It assumes that a higher dose of atorvastatin is relatively more effective by a certain percentage than a lower dose of atorvastatin at reducing the risk of all CV events (apart from the risk of heart failure, which we have assumed in unchanged by any statin). For example, in the first analysis, atorvastatin 20 mg reduces the risk of stroke by the standard rate of 20% (RR: 0.80) as found in the clinical review, and atorvastatin 40 mg is assumed to be 1% relatively more effective and so to reduce stroke by 20.2% (RR: 79.8%).

This analysis does however still assume an equal rate of adverse events for different doses of atorvastatin, which may not be the case.

Table 90: Cost effectiveness of atorvastatin 40 mg compared to atorvastatin 20 mg if atorvastatin 40 mg is 1% more relatively effective

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
High	A20	£11,403	7.480	6.910			
High	A40	£11,450	7.486	**6.914**	£46	0.006	£7,420

Atorvastatin 40 mg would be cost effective compared to atorvastatin 20 mg if its relative effectiveness is 1% greater.

Table 91: Cost effectiveness of atorvastatin 80 mg compared to atorvastatin 40 mg if atorvastatin 80 mg is 1% more relatively effective

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
High	A40	£11,445	7.480	**6.908**			
High	A80	£11,613	7.486	6.906	£168	0.006	£26,828

Atorvastatin 80 mg would not be cost effective compared to atorvastatin 40 mg if its relative effectiveness is 1% greater.

Table 92: Cost effectiveness of atorvastatin 80 mg compared to atorvastatin 40 mg if atorvastatin 80 mg is 2% more relatively effective

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
High	A40	£11,445	7.480	6.908			
High	A80	£11,617	7.493	**6.912**	£172	0.013	£13,759

Atorvastatin 80 mg would be cost effective compared to atorvastatin 40 mg if its relative effectiveness is 2% greater.

Table 93: Cost effectiveness of atorvastatin 80 mg compared to atorvastatin 20 mg if atorvastatin 80 mg is 2% more relatively effective

Class	Drug	Cost	QALYs	Net health benefit	Incr cost	Incr QALY	ICER (per QALY gained)
High	A20	£11,403	7.480	6.910			
High	A80	£11,617	7.493	**6.912**	£214	0.013	£17,122

Atorvastatin 80 mg would be cost effective compared to atorvastatin 20 mg if its relative effectiveness is 2% greater.

In summary, this analysis indicates that, although the relative effectiveness of different atorvastatin doses in reducing the number of CV events is unknown, if there is an increased effectiveness of only 2% between the doses then it would be cost effective to use atorvastatin 80 mg instead of the cheaper atorvastatin 20 mg.

A threshold analysis was not undertaken to compare the cost effectiveness of rosuvastatin (10 mg, 20 mg or 40 mg) with atorvastatin. There is very limited data comparing the effectiveness of rosuvastatin and atorvastatin. The LDL cholesterol reductions shown by atorvastatin 80 mg and rosuvastatin 40 mg are similar,{LAW2003} and the only clinical trial comparing atorvastatin 80 mg to rosuvastatin 40 mg (SATURN{NICHOLLS2011}) reported near identical CV outcomes. (Rosuvastatin 10 mg and 20 mg lower LDL cholesterol less than either rosuvastatin 40 mg or atorvastatin 80 mg do, and would be expected to have lower clinical effectiveness.) As a result there is no basis on which to expect much difference in the clinical effectiveness of rosuvastatin 40 mg compared to atorvastatin 80 mg, but it is much more expensive, and so its use could not be cost effective compared to the use of atorvastatin 80 mg at a cost-effectiveness threshold of £20,000 per QALY gained. Rosuvastatin 10 mg and 20 mg would be expected to be dominated by atorvastatin 80 mg.

L.3.1.4 Cost effectiveness for age and sex subgroups

The base case analysis was repeated for men starting the model aged 40, 50 and 70, and women starting the model aged 40, 50, 60 and 70. All results follow a similar pattern, but with a moderate variation in the magnitude of results.

Results were initially calculated using simvastatin 10 mg, simvastatin 20 mg and atorvastatin 20 mg (the cheapest drugs in each class) as the chosen drug in each class. Following a request by the GDG, results for all subgroups were repeated using atorvastatin 80 mg for high intensity (assuming the same effectiveness as atorvastatin 20 mg), to allow them to judge the implications should they choose atorvastatin 80 mg as the preferred option for secondary prevention.

Table 94: Comparative cost effectiveness of secondary treatment, subgroups

Class	Drug	Cost	QALYs	Net benefit*	Cost	QALYs	Net benefit*
Age 40 at start		**Men**			**Women**		
None	None	£11,611	9.764	9.183	£9,266	9.725	9.261
Low	S10	£13,880	10.231	9.537	£11,421	10.195	9.624
Med	S20	£13,881	10.334	9.640	£11,385	10.298	9.729
High	A20	£14,266	10.585	**9.872**	£11,732	10.552	**9.965**
High	A80	£14,525	10.585	**9.859**	£11,994	10.552	**9.952**
Age 50 at start		**Men**			**Women**		
None	None	£10,720	8.411	7.875	£8,827	8.370	7.928
Low	S10	£12,742	8.843	8.206	£10,769	8.816	8.278
Med	S20	£12,715	8.936	8.301	£10,710	8.913	8.377

Class	Drug	Cost	QALYs	Net benefit*	Cost	QALYs	Net benefit*
High	A20	£13,032	9.158	**8.507**	£11,014	9.144	**8.593**
High	A80	£13,267	9.158	**8.495**	£11,251	9.144	**8.581**
Age 60 at start		**Men**			**Women**		
None	None	£9,501	6.862	6.387	£8,973	6.980	6.531
Low	S10	£11,229	7.230	6.669	£10,714	7.368	6.833
Med	S20	£11,155	7.307	6.749	£10,624	7.450	6.919
High	A20	£11,403	7.480	**6.910**	£10,876	7.639	**7.096**
High	A80	£11,608	7.480	**6.900**	£11,088	7.639	**7.085**
Age 70 at start		**Men**			**Women**		
None	None	£8,656	5.015	4.582	£9,138	5.161	4.705
Low	S10	£10,065	5.315	4.811	£10,649	5.480	4.947
Med	S20	£9,992	5.375	4.876	£10,586	5.543	5.014
High	A20	£10,203	5.502	**4.992**	£10,840	5.685	**5.143**
High	A80	£10,366	5.502	**4.984**	£11,011	5.685	**5.135**

High-intensity statins are cost effective against all other options for all subgroups, whether either atorvastatin 20 mg or atorvastatin 80 mg is chosen as the high-intensity statin. Costs and QALYs are both slightly higher for women, who have a longer life expectancy. ICERs are slightly higher for women and increase with the starting age. ICERs for atorvastatin 20 mg (80 mg) compared to no treatment vary from £2825 (£3132) per QALY gained for women starting at age 50 to £3247 (£3574) per QALY gained for women starting at age 70; all are well below £20,000 per QALY gained.

L.3.1.5 Breakdown of costs by category

The lifetime costs experienced per person are presented in Table 95 for the base case (men, starting at age 60), split into the proportion attributable to the cost of providing statin treatment (including routine monitoring appointments and tests) and the costs attributable to providing healthcare to treat any CV events experienced over the lifetime. The cost of treating CV conditions makes up at least 85% of the costs for all interventions.

Table 95: Lifetime costs per person by category

Class	Drug	Total cost	Lifetime statin costs		Lifetime CV healthcare costs	
None	None	£9,501	£0	0%	£9,501	100%
Low	S10	£11,229	£1,379	12%	£9,850	88%
Med	S20	£11,155	£1,403	13%	£9,752	87%
High	A20	£11,403	£1,503	13%	£9,900	87%
High	A80	£11,608	£1,705	15%	£9,904	85%

L.3.1.6 CV events occurring and averted

The number of subsequent CV events occurring in each arm of the model (excluding the initial event with which all individuals commence the model) is shown in Without any statin treatment the 1000 people in the cohort would be expected to experience 498 non-fatal and 556 fatal CV events (an individual may experience multiple events during their lifetime). With high-intensity statin treatment 143 fewer non-fatal and 95 fewer fatal CV events would be expected.

Table 96 for the base case (men, starting at age 60). The number of events is not affected by the drug chosen within each class since each drug within a class is assumed to have equal effectiveness.

Without any statin treatment the 1000 people in the cohort would be expected to experience 498 non-fatal and 556 fatal CV events (an individual may experience multiple events during their lifetime). With high-intensity statin treatment 143 fewer non-fatal and 95 fewer fatal CV events would be expected.

Table 96: Total subsequent CV events occurring per cohort of 1000 people

Class	Unstable angina	MI	Stroke	Heart failure	Fatal CV event	Total CV events	CV events averted
None	65	191	113	130	556	1054	
Low	53	154	102	133	508	950	104
Med	43	120	90	131	493	877	178
High	33	90	101	131	462	817	237

L.3.2 Primary prevention of CVD

L.3.2.1 Comparative cost effectiveness of different statin classes at set CV risk, as measured by QRISK2 tool

Base case: age 60 at start of model, men and women

As for secondary prevention, these results were originally calculated for simvastatin 10 mg, simvastatin 20 mg and atorvastatin 20 mg, but atorvastatin 80 mg was added on request of the GDG. In all cases it is assumed that once a first CV event occurs for each individual, and they therefore enter the secondary prevention phase of the model, they will all receive atorvastatin 80 mg, in line with the GDG's recommendation for secondary prevention, regardless of the intervention used for primary prevention.

Table 97: Comparative cost effectiveness of different statin classes at set CV risk, as measured by QRISK2 tool

Class	Drug	Costs	QALYs	Net benefit [a]		Costs	QALYs	Net benefit [a]
		Men				**Women**		
QRISK2 10-year risk:		**30% (Total CV risk = 41.9%)**				**30% (Total CV risk = 43.0%)**		
None	None	£6,438	10.156	9.834		£6,720	10.544	10.208
Low	S10	£7,171	10.452	10.093		£7,476	10.868	10.494
Med	S20	£6,808	10.616	10.275		£7,114	11.063	10.708
High	A20	£6,688	10.715	10.381		£7,040	11.166	10.814
High	A80	£6,874	10.715	10.372		£7,232	11.166	10.805
QRISK2 10-year risk:		**25% (Total CV risk = 35.4%)**				**25% (Total CV risk = 36.4%)**		
None	None	£5,704	10.443	10.158		£5,933	10.876	10.580
Low	S10	£6,550	10.725	10.398		£6,804	11.187	10.846
Med	S20	£6,217	10.875	10.564		£6,463	11.366	11.043
High	A20	£6,132	10.959	**10.653**		£6,412	11.456	**11.135**
High	A80	£6,329	10.959	**10.643**		£6,617	11.456	**11.125**
QRISK2 10-year risk:		**20% (Total CV risk = 28.7%)**				**20% (Total CV risk = 29.6%)**		
None	None	£4,899	10.752	10.507		£5,054	11.238	10.985
Low	S10	£5,880	11.014	10.720		£6,067	11.527	11.223
Med	S20	£5,590	11.143	10.864		£5,763	11.684	11.396

Class	Drug	Costs	QALYs	Net benefit [a]		Costs	QALYs	Net benefit [a]
High	A20	£5,549	11.211	**10.933**		£5,742	11.758	**11.471**
High	A80	£5,757	11.211	**10.923**		£5,960	11.758	**11.460**
QRISK2 10-year risk:		**15% (Total CV risk = 21.8%)**				**15% (Total CV risk = 22.5%)**		
None	None	£4,015	11.082	10.882		£4,073	11.633	11.429
Low	S10	£5,157	11.318	11.060		£5,262	11.890	11.627
Med	S20	£4,924	11.423	11.177		£5,011	12.019	11.768
High	A20	£4,935	11.470	**11.223**		£5,029	12.073	**11.822**
High	A80	£5,155	11.470	**11.212**		£5,260	12.073	**11.810**
QRISK2 10-year risk:		**10% (Total CV risk = 14.7%)**				**10% (Total CV risk = 15.2%)**		
None	None	£3,042	11.438	11.286		£2,979	12.062	11.913
Low	S10	£4,377	11.639	11.420		£4,381	12.277	12.058
Med	S20	£4,216	11.714	11.503		£4,202	12.371	12.160
High	A20	£4,291	11.737	**11.522**		£4,269	12.402	**12.189**
High	A80	£4,522	11.737	**11.510**		£4,515	12.402	**12.176**
QRISK2 10-year risk:		**9% (Total CV risk = 13.3%)**				**8% (Total CV risk = 12.2%)**		
None	None	£2,837	11.512	11.370		£2,508	12.245	12.119
Low	S10	£4,214	11.705	11.494		£4,006	12.439	12.239
Med	S20	£4,070	11.773	11.570		£3,863	12.516	12.323
High	A20	£4,158	11.791	**11.583**		£3,952	12.538	**12.340**
High	A80	£4,392	11.791	**11.571**		£4,203	12.538	**12.328**
QRISK2 10-year risk:		**8% (Total CV risk = 11.8%)**				**7% (Total CV risk = 10.7%)**		
None	None	£2,627	11.587	11.456		£2,264	12.338	12.225
Low	S10	£4,048	11.772	11.570		£3,814	12.522	12.331
Med	S20	£3,921	11.833	11.637		£3,689	12.590	12.406
High	A20	£4,024	11.846	**11.645**		£3,790	12.607	**12.417**
High	A80	£4,260	11.846	11.633		£4,045	12.607	12.404
QRISK2 10-year risk:		**7% (Total CV risk = 10.4%)**				**6% (Total CV risk = 9.2%)**		
None	None	£2,413	11.664	11.543		£2,015	12.434	12.333
Low	S10	£3,880	11.840	11.646		£3,619	12.606	12.425
Med	S20	£3,771	11.894	11.705		£3,513	12.665	12.489
High	A20	£3,888	11.901	**11.706**		£3,626	12.676	**12.495**
High	A80	£4,127	11.901	11.695		£3,884	12.676	12.482
QRISK2 10-year risk:		**6% (Total CV risk = 8.9%)**				**5% (Total CV risk = 7.7%)**		
None	None	£2,196	11.741	11.631		£1,760	12.530	12.442
Low	S10	£3,709	11.908	11.723		£3,419	12.691	12.520
Med	S20	£3,619	11.955	**11.774**		£3,335	12.741	**12.574**
High	A20	£3,752	11.956	11.769		£3,460	12.746	12.573
High	A80	£3,993	11.956	11.757		£3,721	12.746	12.560

(a) At a cost-effectiveness threshold of £20,000 per QALY gained

Medium-intensity treatment dominates low-intensity treatment and is cost effective compared to no treatment down to a risk of 6% or even lower.

High-intensity statin treatment using atorvastatin 20 mg (80 mg) is cost effective at a threshold of £20,000 per QALY gained compared to medium-intensity statins at QRISK2 scores above 6.8% (8.7%) for men aged 60. At 10% the ICERs are £3,227per QALY gained for men age 60 (£2,108 for women age 60) for atorvastatin 20 mg compared to simvastatin 20 mg, and £13,253 per QALY gained for men (£9,881 for women) for atorvastatin 80 mg compared to simvastatin 20 mg.

The analysis was rerun probabilistically at a QRISK2 score of 10% for men starting at age 60 years. The results are shown in Table 98 and The results are again similar to the deterministic results in the previous table. The ICERs for high-intensity statins compared to no treatment were £4,125 per QALY gained (deterministic: £4,177) for atorvastatin 20 mg and £4,875 per QALY gained (deterministic: £4,951) for atorvastatin 80 mg.

When the 4 classes of intervention were compared, with atorvastatin 20 mg as the high-intensity statin, high intensity was cost effective in 74.5% of 1000 simulations, and medium intensity in 25.5% of simulations.

Figure 167.

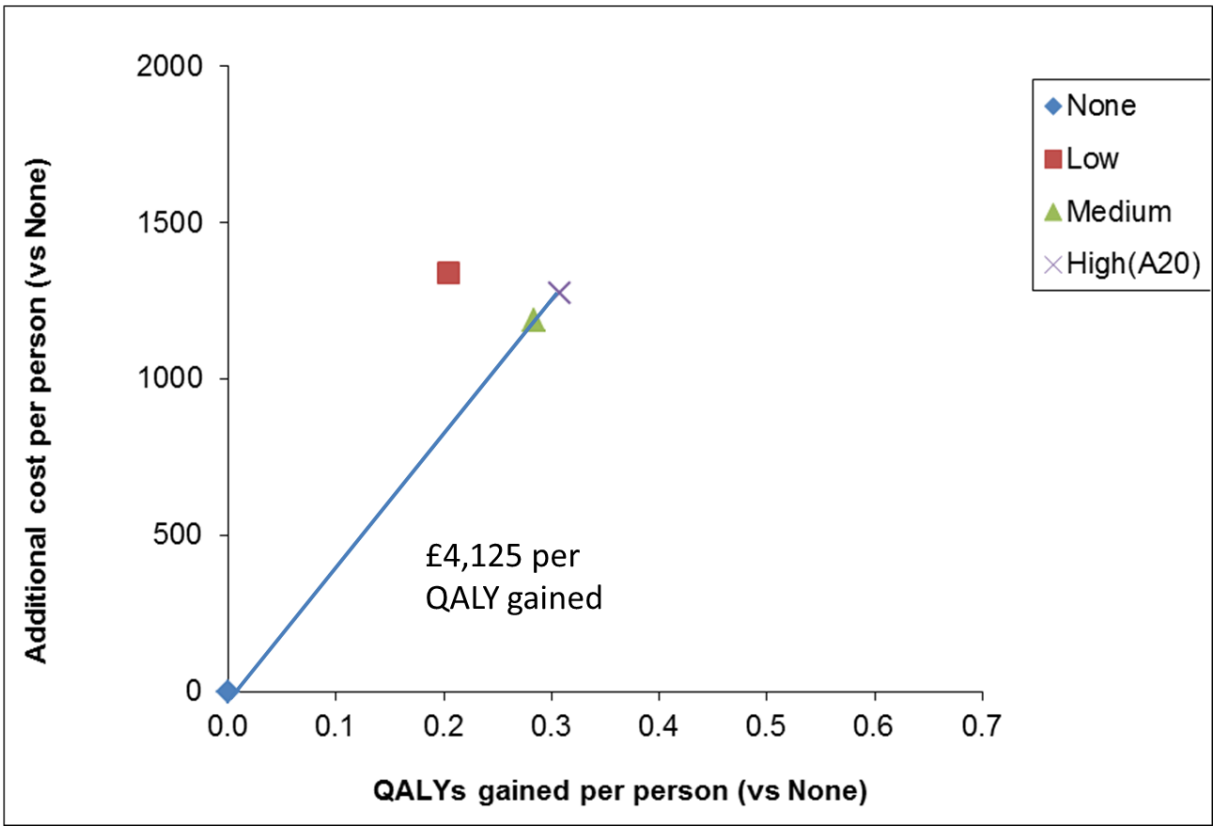
Table 98: Comparative cost effectiveness of different statin classes at 10% risk, as measured by QRISK2 tool (14.7% total CV risk): probabilistic analysis

Class	Drug	Costs	QALYs	Net health benefit	Rank of net benefit (95% CI)
None	None	£3,013	11.414	11.264	4 (4 to 4)
Low	S10	£4,353	11.619	11.401	3 (3 to 3)
Med	S20	£4,199	11.698	11.488	2 (1 to 2)
High	A20	£4,285	11.723	**11.508**	1 (1 to 2)
High	A80	£4,516	11.723	11.497	

The results are again similar to the deterministic results in the previous table. The ICERs for high-intensity statins compared to no treatment were £4,125 per QALY gained (deterministic: £4,177) for atorvastatin 20 mg and £4,875 per QALY gained (deterministic: £4,951) for atorvastatin 80 mg.

When the 4 classes of intervention were compared, with atorvastatin 20 mg as the high-intensity statin, high intensity was cost effective in 74.5% of 1000 simulations, and medium intensity in 25.5% of simulations.

Figure 167: Cost effectiveness of statins for primary prevention at a QRISK2 score of 10% (probabilistic)



L.3.2.2 Comparative cost effectiveness of different statin classes at set CV risk, as measured by QRISK2 tool: subgroup analysis

The analysis was repeated for all age and sex subgroups at a QRISK2 score of 10%:

Table 99: Comparative cost effectiveness of different statin classes at set CV risk, as measured by QRISK2 tool – subgroup analysis

Class	Drug	Costs	QALYs	Net benefit		Costs	QALYs	Net benefit
		Men				**Women**		
Age 40 at start		**QRISK 10% (Total CV risk = 15.6%)**				**QRISK 10% (Total CV risk = 16.3%)**		
None	None	£5,696	14.699	14.414		£5,165	15.179	14.921
Low	S10	£7,029	14.956	14.605		£6,585	15.451	15.121
Med	S20	£6,622	15.101	14.770		£6,190	15.618	15.308
High	A20	£6,603	15.202	**14.872**		£6,213	15.736	**15.426**
High	A80	£6,893	15.202	**14.857**		£6,516	15.736	**15.411**
Age 50 at start		**QRISK 10% (Total CV risk = 15.6%)**				**QRISK 10% (Total CV risk = 16.3%)**		
None	None	£4,360	13.306	13.088		£4,020	13.820	13.619
Low	S10	£5,742	13.538	13.251		£5,474	14.069	13.796
Med	S20	£5,472	13.649	13.375		£5,196	14.205	13.945
High	A20	£5,522	13.703	**13.427**		£5,240	14.275	**14.013**
High	A80	£5,787	13.703	**13.414**		£5,520	14.275	**13.999**
Age 60 at start		**QRISK 10% (Total CV risk = 14.7%)**				**QRISK 10% (Total CV risk = 15.2%)**		

Class	Drug	Costs	QALYs	Net benefit		Costs	QALYs	Net benefit
None	None	£3,042	11.438	11.286		£2,979	12.062	11.913
Low	S10	£4,377	11.639	11.420		£4,381	12.277	12.058
Med	S20	£4,216	11.714	11.503		£4,202	12.371	12.160
High	A20	£4,291	11.737	**11.522**		£4,269	12.402	**12.189**
High	A80	£4,522	11.737	**11.510**		£4,515	12.402	**12.176**
Age 70 at start		**QRISK 10% (Total CV risk = 13.9%)**				**QRISK 10% (Total CV risk = 14.5%)**		
None	None	£1,922	9.045	8.949		£1,967	9.759	9.661
Low	S10	£3,067	9.215	9.062		£3,195	9.936	9.776
Med	S20	£2,970	9.259	9.111		£3,090	9.991	9.836
High	A20	£3,024	9.271	**9.120**		£3,155	10.001	**9.843**
High	A80	£3,210	9.271	9.111		£3,356	10.001	9.833

Atorvastatin 20 mg is dominant or cost effective at a threshold of £20,000 per QALY gained compared to medium-intensity simvastatin 20 mg for all the subgroups. Atorvastatin 80 mg is cost effective compared to simvastatin 20 mg for all the subgroups except for men and women aged 70 years.

L.3.2.3 Breakdown of costs by category

The lifetime costs experienced per person are presented in conditions (£2392–£2762) are much lower than in secondary prevention (£9501–£9904). These costs are lower with statin treatment than with no treatment, despite increased longevity, due to the reduction in CV events caused by statins. The cost of treating CV conditions still makes up the majority of the costs for all interventions, but statin costs comprise almost half of the costs in the case of atorvastatin 80 mg, compared to 15% of costs in secondary prevention.

Table 100 for the base case (men, starting at age 60 with QRISK2 CV risk score of 10% and receiving atorvastatin 80 mg for secondary prevention in all arms following a first CV event). These are split into the proportion attributable to the cost of providing statin treatment (including routine monitoring appointments and tests) for both primary and secondary prevention and the costs attributable to providing healthcare to treat any CV events experienced over the lifetime. The lifetime costs of providing statins (£281–£2126 per person) are slightly higher than the equivalent costs for people in secondary prevention (£0–£1705, see sSection L.3.1.5). By contrast the lifetime costs of treating CV conditions (£2392–£2762) are much lower than in secondary prevention (£9501–£9904). These costs are lower with statin treatment than with no treatment, despite increased longevity, due to the reduction in CV events caused by statins. The cost of treating CV conditions still makes up the majority of the costs for all interventions, but statin costs comprise almost half of the costs in the case of atorvastatin 80 mg, compared to 15% of costs in secondary prevention.

Table 100: Lifetime costs per person by category

Class	Drug	Total cost	Lifetime statin costs		Lifetime CV healthcare costs	
None	None	£3,042	£281	9%	£2,762	91%
Low	S10	£4,377	£1,810	41%	£2,567	59%
Med	S20	£4,216	£1,822	43%	£2,394	57%
High	A20	£4,291	£1,899	44%	£2,392	56%
High	A80	£4,522	£2,126	47%	£2,396	53%

L.3.2.4 CV events occurring and averted

The total number of CV events occurring in each arm of the model (both initial and subsequent events) is shown in Without any statin treatment the 1000 people in the cohort would be expected to experience 483 non-fatal and 168 fatal CV events (an individual may experience multiple events during their lifetime). With high-intensity statin treatment 84 fewer non-fatal and 27 fewer fatal CV events would be expected.

Table 101 for the base case (men, starting at age 60 with QRISK2 CV risk score of 10% and receiving atorvastatin 80 mg for secondary prevention in all arms following a first CV event). The number of events is not affected by the drug chosen within each class since each drug within a class is assumed to have equal effectiveness.

Without any statin treatment the 1000 people in the cohort would be expected to experience 483 non-fatal and 168 fatal CV events (an individual may experience multiple events during their lifetime). With high-intensity statin treatment 84 fewer non-fatal and 27 fewer fatal CV events would be expected.

Table 101: Total subsequent CV events occurring per cohort of 1000 people

Class	Stable angina	Unstable angina	MI	TIA	Stroke	Heart failure	PAD	Fatal CV event	Total	CV events averted
None	66	33	75	23	120	104	61	168	651	
Low	54	27	62	20	109	112	50	151	586	65
Med	43	22	50	18	100	119	40	142	535	116
High	32	18	40	23	124	132	30	141	540	111

L.3.2.5 Comparative cost effectiveness of different statin classes at set CV risk, as measured by UKPDS tool

The primary prevention model was rerun with risk measured using the UKPDS risk tool.

Table 102: Comparative cost effectiveness of different statin classes at set CV risk, as measured by UKPDS tool

Class	Drug	Costs	QALYs	Net benefit		Costs	QALYs	Net benefit
		Men				**Women**		
UKPDS 10-year risk:		**30% (Total CV risk = 66.3%)**				**30% (Total CV risk = 69.7%)**		
None	None	£8,578	9.263	8.834		£8,817	9.584	9.144
Low	S10	£9,014	9.577	9.126		£9,264	9.931	9.468
Med	S20	£8,600	9.770	9.340		£8,862	10.161	9.718
High	A20	£8,392	9.907	**9.488**		£8,725	10.302	**9.865**
High	A80	£8,543	9.907	**9.480**		£8,880	10.302	**9.858**
UKPDS 10-year risk:		**25% (Total CV risk = 58.2%)**				**25% (Total CV risk = 61.5%)**		
None	None	£7,781	9.596	9.207		£7,986	9.959	9.560
Low	S10	£8,304	9.913	9.497		£8,521	10.310	9.884
Med	S20	£7,892	10.102	9.707		£8,111	10.537	10.131
High	A20	£7,705	10.229	**9.844**		£7,983	10.668	**10.269**
High	A80	£7,870	10.229	**9.835**		£8,154	10.668	**10.261**
UKPDS 10-year risk:		**20% (Total CV risk = 48.9%)**				**20% (Total CV risk = 52.0%)**		
None	None	£6,835	9.981	9.639		£6,983	10.398	10.048

Class	Drug	Costs	QALYs	Net benefit		Costs	QALYs	Net benefit
Low	S10	£7,482	10.290	9.916		£7,648	10.742	10.359
Med	S20	£7,091	10.467	10.112		£7,250	10.954	10.591
High	A20	£6,940	10.578	**10.231**		£7,145	11.071	**10.713**
High	A80	£7,121	10.578	**10.222**		£7,333	11.071	**10.704**
UKPDS 10-year risk:		**15% (Total CV risk = 38.5%)**				**15% (Total CV risk = 41.2%)**		
None	None	£5,707	10.425	10.140		£5,772	10.911	10.622
Low	S10	£6,528	10.714	10.388		£6,623	11.231	10.900
Med	S20	£6,183	10.868	10.559		£6,266	11.417	11.103
High	A20	£6,088	10.956	**10.652**		£6,200	11.512	**11.202**
High	A80	£6,285	10.956	**10.642**		£6,408	11.512	**11.191**
UKPDS 10-year risk:		**10% (Total CV risk = 26.9%)**				**10% (Total CV risk = 29.0%)**		
None	None	£4,359	10.940	10.722		£4,308	11.512	11.297
Low	S10	£5,419	11.191	10.920		£5,422	11.787	11.516
Med	S20	£5,154	11.309	11.052		£5,142	11.930	11.673
High	A20	£5,136	11.367	**11.110**		£5,135	11.995	**11.738**
High	A80	£5,351	11.367	**11.099**		£5,363	11.995	**11.727**
UKPDS 10-year risk:		**5% (Total CV risk = 14.1%)**				**5% (Total CV risk = 15.3%)**		
None	None	£2,742	11.537	11.400		£2,539	12.216	12.089
Low	S10	£4,129	11.729	11.522		£4,014	12.417	12.217
Med	S20	£3,987	11.796	11.596		£3,860	12.499	12.306
High	A20	£4,075	11.812	**11.609**		£3,937	12.525	**12.328**
High	A80	£4,310	11.812	**11.597**		£4,188	12.525	**12.315**
UKPDS 10-year risk:		**4% (Total CV risk = 11.4%)**				**4% (Total CV risk = 12.3%)**		
None	None	£2,381	11.667	11.548		£2,143	12.371	12.264
Low	S10	£3,846	11.844	11.652		£3,705	12.553	12.368
Med	S20	£3,736	11.898	11.712		£3,583	12.620	12.441
High	A20	£3,848	11.906	**11.714**		£3,679	12.637	**12.453**
High	A80	£4,087	11.906	11.702		£3,936	12.637	12.440
UKPDS 10-year risk:		**3.6% (Total CV risk = 10.3%)**				**3% (Total CV risk = 9.3%)**		
None	None	£2,233	11.721	11.609		£1,732	12.530	12.444
Low	S10	£3,731	11.891	11.705		£3,386	12.693	12.523
Med	S20	£3,633	11.940	**11.759**		£3,298	12.744	12.579
High	A20	£3,756	11.944	11.756		£3,416	12.750	**12.580**
High	A80	£3,997	11.944	11.744		£3,677	12.750	12.567
UKPDS 10-year risk:						**2% (Total CV risk = 6.3%)**		
None	None					£1,306	12.695	12.630
Low	S10					£3,057	12.835	12.683
Med	S20					£3,006	12.870	**12.719**
High	A20					£3,147	12.866	12.709
High	A80					£3,413	12.866	12.696

The results are similar to those for QRISK2, though slightly different as UKPDS scores are lower than the equivalent QRISK2 scores. Medium-intensity treatment again dominates low-intensity treatment and is cost effective compared to no treatment at risk levels down to a risk of 5% or even lower.

High-intensity statin treatment using atorvastatin 20 mg (80 mg) is cost effective at a threshold of £20,000 per QALY gained compared to medium-intensity statins at UKPDS scores above 3.9% (5.0%) for men aged 60. At 10% UKPDS risk atorvastatin 20 mg dominates simvastatin 20 mg, and the ICERs for atorvastatin 80 mg compared to simvastatin 20 mg are £3,445 per QALY gained for men aged 60 and £3,416 for women aged 60.

L.3.3 Sensitivity analyses

L.3.3.1 Adverse events scenario analysis

For the first analysis we investigated the impact if 5% of those who started statin treatment with either atorvastatin 80 mg or atorvastatin 20 mg were to cease taking any statin and another 5% were to switch to medium-intensity atorvastatin 10 mg; compared to those who started treatment with atorvastatin 10 mg, of whom we assumed 2% would stop and 2% switch to low-intensity simvastatin 10 mg. Using this high-intensity strategy atorvastatin 20 mg still extendedly dominates the medium-intensity strategy and atorvastatin 80 mg is still cost effective compared to the medium-intensity strategy (ICER: £15,096 per QALY gained compared to £11,865 per QALY gained in the base case where no patients drops out or changes treatment). These rates of change of treatment are much higher than the rates of adverse events seen in clinical trials. It should also be noted that if an individual experiences an adverse event whilst taking atorvastatin 80 mg or 40 mg they should be advised to change to atorvastatin 40 mg or 20 mg in the first instance, and would only be recommended to try a medium-intensity statin (atorvastatin 10 mg) if an adverse event is experienced with the second dose tried as well.

For the second analysis we investigated the impact if 10% of those taking high-intensity statins ceased taking any statin and another 10% switched to medium-intensity statins; whilst for medium-intensity statins 5% stopped and 5% switched to low-intensity statins. In this scenario atorvastatin 20 mg dominated medium-intensity statins, whilst atorvastatin 80 mg remained cost effective compared with medium-intensity statins (ICER: £18,807 per QALY gained).

L.3.3.2 One-way deterministic sensitivity analyses

One-way sensitivity analyses were conducted as specified in the methods.

All analyses were conducted using a cohort of men with starting age of 60. For primary prevention the cost effectiveness for a cohort at a QRISK2 risk score of 10% was investigated. In each case the results recorded are the ICERs for medium-intensity treatment (simvastatin 20 mg) against no treatment (NT) and for high-intensity treatment (both atorvastatin 20 mg and atorvastatin 80 mg) against medium-intensity treatment. Medium-intensity treatment dominated low-intensity treatment under all scenarios and so this is not shown in the table below.

Table 103: One-way deterministic sensitivity analyses (men, starting at age 60)

Parameter		Secondary prevention: ICERs				Primary prevention (QRISK2 10%): ICERs		
	Variation	S20 vs NT	A20 vs S20	A80 vs S20		S20 vs NT	A20 vs S20	A80 vs S20
BASE CASE		**£3,716**	**£1,436**	**£2,621**		**£4,257**	**£3,227**	**£13,253**
Costs of all health states								
	+100%	£4,203	£2,224	£3,409		£2,807	£2,818	£12,844
	−50%	£3,473	£1,042	£2,227		£4,981	£3,431	£13,458

Parameter		Secondary prevention: ICERs				Primary prevention (QRISK2 10%): ICERs		
	Variation	S20 vs NT	A20 vs S20	A80 vs S20		S20 vs NT	A20 vs S20	A80 vs S20
	Monitoring appoint-ment costs	£1,918	£1,323	£2,508		£1,043	£3,132	£13,159
Utility multipliers for all health states								
	Upper CIs	£3,415	£1,304	£2,380		£4,681	£3,726	£15,305
	Lower CIs	£4,076	£1,598	£2,916		£3,903	£2,845	£11,687
Baseline utility assumed to be constant (no decrease in quality of life with age)								
	1.0 for all ages	£2,743	£1,061	£1,936		£3,088	£2,527	£10,381
Discount rate for costs and benefits								
	1.5%	£3,475	£1,462	£2,521		£3,602	£5,301	£16,606
Baseline transition probabilities								
	−10%	£3,939	£1,456	£2,742		£4,839	£5,096	£18,724
	−20%	£4,209	£1,484	£2,894		£5,533	£8,906	*£29,723*
Risk ratios								
	RR1	£5,556	£943	*Dominated*		£9,624	*Dominated*	*Dominated*
	RR2	£2,980	£1,441	£2,095		£2,723	£2,577	£8,002
	RR3	£3,774	£1,284	£2,443		£4,597	£755	£6,081
	RR4	£3,774	£1,518	£3,785		£4,491	£1,967	£11,948
	RR5	£3,716	£1,145	£3,291		£4,221	Dominates	£4,189
	RR6	£3,592	£1,048	£3,199		£3,570	*Dominated*	*Dominated*
	RR7	£3,649	£1,331	£2,846		£4,695	Dominates	£4,123
Duration of effective statin treatment								
	20 years	£3,613	£1,413	£2,550		£3,720	£449	£6,578
	10 years	£3,460	£1,367	£2,457		£3,004	Dominates	£2,471
	5 years	£3,442	£1,439	£2,526		£2,392	Dominates	£1,380
	1 year	£2,550	£1,032	£1,866		£1,278	Dominates	£796
Continuance with treatment (50% drop-out after 1 year)								
		£3,529	£1,396	£2,546		£3,534	£2,154	£10,509
Type 2 diabetes (additional cases rather than earlier onset)								
	25%	£3,787	£1,677	£2,869		£4,339	£4,517	£14,816
	100%	£3,999	£2,402	£3,614		£4,587	£8,784	£19,996
Allow patients to transition out of PAD and heart failure states								
		£3,938	£1,552	£2,887		£4,216	£2,987	£13,099

High-intensity statins were cost effective in all scenarios apart from RR1 (if all the risk ratios are taken to be at the end of their range), RR6 (if the rate of non-CV death was not constant between statin classes), and, in the case of atorvastatin 80 mg for primary prevention, a reduction in all baseline transition probabilities of 20%. The results are very sensitive to the rate of non-CV death in primary prevention (only) because a large majority of people undergoing primary prevention will ultimately die of a non-CV cause, and so anything which increases that death rate in relative terms is highly detrimental. The GDG agreed that there is no evidence that high-intensity statins do have a different effect on non-CV death than medium-intensity statins, but we accept that if that was to be the case then medium-intensity statins should be preferred.

The results are not sensitive to the costs of health states, utility multipliers for health states, the use of age-related utilities, discount rates of 1.5%, duration of effective statin treatment, high rates of discontinuance, whether the model allowed transitions out of the PAD and heart failure states or the proportion of excess cases of diabetes diagnosed in people taking statins which represent entirely additional cases of diabetes rather than expected cases starting earlier.

L.3.3.3 Cost-effectiveness threshold

For secondary prevention, the ICERs for high-intensity treatment were all comfortably below £20,000 per QALY gained for all subgroups and in almost all one-way sensitivity analyses. Therefore raising the cost-effectiveness threshold to £30,000 per QALY gained would have no effect – high-intensity statins would remain the preferred treatment.

For primary prevention the ICERs for treatment depend on the level of CV risk, and so the result of increasing the cost-effectiveness threshold from £20,000 to £30,000 per QALY gained is to reduce the risk level at which treatment is cost effective. Table 104 below shows the CV risks, as measured by QRISK2, above which high-intensity statin treatment using atorvastatin 20 mg, 40 mg or 80 mg is cost effective compared to medium-intensity statin treatment using simvastatin 20 mg. The columns on the right show the comparative risk thresholds if the cost-effectiveness threshold is increased to £30,000 per QALY gained.

The primary prevention model does not work at very low levels of CV risk due to the effect of the negative component of age-related risk which is added to early years of the model. Values written in lighter type denote risks below the level at which the model is entirely accurate; these values are indicative of the likely risk thresholds, but should not be relied on.

Table 104: Risk thresholds using QRISK2 at which high-intensity primary prevention treatment is cost effective compared to medium-intensity treatment (simvastatin 20 mg) for different cost-effectiveness thresholds

	Risk threshold above which high-intensity statins are cost effective					
	£20,000 per QALY gained			£30,000 per QALY gained		
	A20	A40	A80	A20	A40	A80
Men age 40	3.1%	3.3%	4.0%	2.9%	3.0%	3.5%
Men age 50	5.0%	5.3%	6.3%	4.8%	5.0%	5.7%
Men age 60	6.8%	7.1%	8.7%	6.4%	6.7%	7.8%
Men age 70	6.8%	7.5%	10.1%	6.4%	6.8%	8.6%
Women age 40	2.4%	2.6%	3.4%	2.2%	2.3%	2.9%
Women age 50	3.5%	3.8%	4.8%	3.3%	3.5%	4.2%
Women age 60	5.2%	5.6%	7.2%	4.8%	5.1%	6.3%
Women age 70	7.3%	8.1%	11.6%	6.7%	7.3%	9.6%

L.4 Discussion

L.4.1 Summary of results

L.4.1.1 Secondary prevention

This analysis finds that high-intensity statin treatment using atorvastatin 20 mg, 40 mg or 80 mg is cost effective compared to medium- and low-intensity statin treatment and compared to no

treatment for people who already have CVD (ICER: £2959 per QALY gained for atorvastatin 20 mg compared to no treatment; £3275 per QALY gained for atorvastatin 80 mg compared to no treatment). These results were robust to all the sensitivity analyses conducted and for all subgroups by age and sex.

The base case analysis was based on an assumption of equivalent effectiveness between all high-intensity statins, due to a lack of evidence comparing the effectiveness of the different doses within the high-intensity class in terms of reducing clinical end points, although there is evidence of differing effectiveness of different doses in terms of reducing LDL cholesterol levels. On this basis the cheapest high-intensity statin – atorvastatin 20 mg – was predicted to be the most cost effective. However, an additional threshold analysis showed that atorvastatin 40 mg would be cost effective compared to atorvastatin 20 mg if it was 1% relatively more effective in decreasing CV events than atorvastatin 20 mg and if there was no loss in utility due to increases in adverse events. It also showed that atorvastatin 80 mg would be cost effective compared to atorvastatin 20 mg if it was 2% relatively more effective than atorvastatin 20 mg in decreasing CV events and if there was no loss in utility due to increases in adverse events.

L.4.1.2 Primary prevention

This analysis finds that high-intensity statin treatment using atorvastatin 20 mg is cost effective compared to medium-intensity statin treatment using simvastatin 20 mg at a cost-effectiveness threshold of £20,000 per QALY gained for men aged 60 who do not have CVD and who have a QRISK2 CV risk score above 6.8%. Atorvastatin 80 mg is cost effective compared to medium-intensity statins for those men aged 60 who have a QRISK2 score above 8.7%. Medium-intensity treatment is cost effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest. At a QRISK2 risk score of 10% the ICERs compared to medium-intensity simvastatin 20 mg treatment were £3~~,~~438 per QALY gained for atorvastatin 20 mg and £12,769 per QALY gained for atorvastatin 80 mg. The results for atorvastatin 20 mg versus simvastatin 20 mg at a QRISK2 score of 10% were robust for all subgroups and almost all sensitivity analyses.

These results do not include the potential effects of adverse events other than an increase in cases of type 2 diabetes. A scenario analysis was therefore carried out considering the impact if a greater rate of adverse events in high-intensity treatment caused some people to cease taking statins or to change to a lower intensity. This found that high-intensity treatment would still be cost effective compared to medium-intensity treatment if 10% of people taking high-intensity statins ceased treatment and another 10% switched to a medium-intensity statin, demonstrating that the results are insensitive to the rates of adverse events over a very wide range of possible rates.

L.4.1.3 Type 2 diabetes

This analysis finds that high-intensity statin treatment using atorvastatin 20 mg is cost effective compared to medium-intensity statin treatment at a cost-effectiveness threshold of £20,000 per QALY gained for people who have type 2 diabetes but do not have CVD and who have a UKPDS CV risk score above 3.9%. Atorvastatin 80 mg is cost effective compared to medium-intensity statins for those who have a UKPDS~~QRISK2~~ score above 5.0%. Medium-intensity treatment is cost effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest. At a UKPDS risk score of 10% atorvastatin 20 mg dominated simvastatin 20 mg and atorvastatin 80 mg had an ICER of £3~~,~~445 per QALY gained compared with simvastatin 20 mg.

L.4.2 Comparisons with published studies

These results are largely consistent with previous published cost-effectiveness analyses, but support the use of higher-intensity statins than some previous studies have done due to the recent decrease in statin costs, notably of atorvastatin.

The model by Ward et al (2005)[1406] for technology appraisal 94 (2006), [1007] which this guideline updates, found that statins as a single class were cost effective compared to placebo for secondary prevention but did not differentiate between different statins. Clinical guideline 67 (2008),[1004] which this guideline also updates, found that high-intensity statins were cost effective compared to medium-intensity statins in secondary prevention for people with ACS but not routinely for those with CHD, although a strategy of increasing the statin dose in those people with CHD who had received insufficient benefit from medium-intensity statins could be justified. The most recent economic analysis of statins for secondary prevention appraised for this guideline (Ara et al. 2009{ARA2009}) carried out an analysis with a projected lower future cost of atorvastatin 80 mg in anticipation of the reduction in price of atorvastatin after its patent was due to expire in 2012. That study reached the same conclusion as this new analysis – that atorvastatin 80 mg is cost effective for secondary prevention at a cost-effectiveness threshold of £20,000 per QALY gained.

For primary prevention Ward again looked only at the cost effectiveness of statins as a single class, and found that the CV risk threshold at which statins were cost effective varied considerably between age and sex subgroups and under sensitivity analyses, although all risk thresholds were raised by the much higher price of statins used in the model, and the results are complicated by the different discount rates used in that model. Choudhry et al. 2011{CHOUDHRY2011} looked at the cost effectiveness of high-intensity rosuvastatin compared with placebo (but not compared with other, cheaper, high-intensity statins) in a population similar to the JUPITER study (that is, people with low LDL cholesterol but raised high-sensitivity C-reactive protein). This study found that rosuvastatin 20 mg had marginal cost effectiveness compared to a cost-effectiveness threshold of £20,000 per QALY gained, with the ICERs for some population subgroups below this level while other subgroups or sensitivity analyses producing results above this level. This is consistent with our conclusion that rosuvastatin is not as cost effective as high-intensity doses of atorvastatin due to its higher cost, although its applicability is limited due to the distinctive population studied. The final economic evaluation considered, McConnachie et al. 2014{MCCONNACHIE2014} is a follow-up study investigating the cost effectiveness of 5 years of treatment with pravastatin 40 mg in Scottish men followed by 10 years of further routine care (with similar use of statins in both groups), and finds that the intervention was cost saving over the 15 years, dominating no treatment. The paper uses recent UK costs and was found to be directly applicable to the current UK context. It is consistent with the sensitivity analysis in this model for reduced length of treatment, which found that 5 years of treatment was highly cost effective for medium-intensity statins compared with no treatment, and that high-intensity statins (atorvastatin 20 mg) were dominant compared to medium-intensity statins.

See Section 11.8.1 of the guideline for further discussion of previous studies.

L.4.3 Conclusions

- One original cost–utility analysis found that
  - high-intensity statins were cost effective compared to no treatment for the **secondary prevention** of CVD in men aged 60 (ICER: £2959 per QALY gained for atorvastatin 20 mg; £3275 per QALY gained for atorvastatin 80 mg)
  - medium- and low-intensity statins were subject to extended dominance by high-intensity statins and no treatment.

  This analysis was assessed as directly applicable with minor limitations.
- One original cost–utility analysis found that
  - high-intensity statins were cost effective compared to no treatment for the **primary prevention** of CVD in men aged 60 at a **QRISK score of 10%** (ICER: £4125 per QALY gained for atorvastatin 20 mg; £4875 per QALY gained for atorvastatin 80 mg)

  - medium-intensity statins were subject to extended dominance by high-intensity statins and no treatment in the case of atorvastatin 20 mg; high-intensity statins were cost effective compared to medium-intensity statins in the case of atorvastatin 80 mg (ICER: £12,769 per QALY gained)
  - low-intensity statins were dominated by high-intensity statins.

  This analysis was assessed as directly applicable with minor limitations.

- One original cost–utility analysis found that

high-intensity statins were cost effective compared to no treatment for the primary prevention of CVD in men aged 60 **with type 2 diabetes** at a **UKPDS score of 10%** (ICER: £1822 per QALY gained for atorvastatin 20 mg; £2326 per QALY gained for atorvastatin 80 mg)

  - high-intensity statins dominated medium-intensity statins in the case of atorvastatin 20 mg and were cost effective compared to medium-intensity statins in the case of atorvastatin 80 mg (ICER: £3445 per QALY gained)
  - low-intensity statins were dominated by high-intensity statins.

  This analysis was assessed as directly applicable with minor limitations.

Appendix M: Unit costs

M.1 Statins

Statin	Daily dose	Cost – 28 days	Cost – annual
Fluvastatin	20 mg	£2.27	£29.61
Fluvastatin	40 mg	£2.37	£30.92
Fluvastatin	80 mg[(a)]	£4.74	£61.83
Pravastatin	10 mg	£1.16	£15.13
Pravastatin	20 mg	£1.41	£18.39
Pravastatin	40 mg	£1.77	£23.09
Simvastatin	10 mg	£0.80	£10.44
Simvastatin	20 mg	£0.86	£11.22
Simvastatin	40 mg	£1.09	£14.22
Simvastatin	80 mg[(b)]	£1.65	£21.52
Atorvastatin	10 mg	£1.03	£13.44
Atorvastatin	20 mg	£1.26	£16.44
Atorvastatin	40 mg	£1.51	£19.70
Atorvastatin	80 mg	£2.48	£32.35
Rosuvastatin (Crestor)[(c)]	5 mg	£18.03	£235.19
Rosuvastatin (Crestor)[(c)]	10 mg	£18.03	£235.19
Rosuvastatin (Crestor)[(c)]	20 mg	£26.02	£339.42
Rosuvastatin (Crestor)[(c)]	40 mg	£29.69	£387.30

Source: NHS Drug Tariff, May 2014[1021]

Fluvastatin 10 mg, pravastatin 80 mg and rosuvastatin 80 mg are not available in the UK and so are not listed.

(a) Fluvastatin 80 mg is only available in a modified release formulation (£19.20 for 28 days, £250.46 annually). The costs given here are for taking 2 fluvastatin 40 mg tablets per day.

(b) The MHRA advises that, due to an increased risk of myopathy, an 80 mg dose of simvastatin should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

(c) Rosuvastatin is under patent in the UK until June 2017. The prices for all other drugs are for generic formulations.

M.2 Fibrates

Fibrate	Daily dose	Cost – 28 days	Cost – annual
Bezafibrate	600 mg	£4.33	£56.43
Bezafibrate modified release	400 mg	£3.25	£42.40
Ciprofibrate	100 mg	£84.91	£1107.62
Fenofibrate (micronised)	200 mg	£1.88	£24.52
Gemfibrozil	1.2 g	£34.75	£453.30

Sources: NHS Drug Tariff, May 2014[1021]*; British National Formulary, May 2014*[717]

M.3 Bile acid sequestrants

Bile acid sequestrant	Daily dose	Cost – 28 days	Cost – annual
Colesevelam hydrochloride (Cholestagel)	3.75 g	£89.69	£1170

Bile acid sequestrant	Daily dose	Cost – 28 days	Cost – annual
Colestyramine (Questran)[(a)]	12–24 g	£18.08–£36.15	£236–£472
Colestipol hydrochloride (Colestid)	10–30 g	£28.09–£84.28	£366–£1099

Sources: NHS Drug Tariff, May 2014[1021]; British National Formulary, May 2014[717]
(a) A sugar-free generic formulation of colestyramine is available, but this is more expensive than the branded version

M.4 Pharmaceutical preparations of omega-3 fatty acids

Omega-3 product	Contents (1 capsule)	Licensing	Daily dose	Cost (28 days)	Cost (annual)
Omacor	460 mg EPA, 380 mg DHA (1 g)	Secondary prevention <3 months after MI or hypertriglyceridaemia	Following MI: 1 capsule Hypertriglyceridaemia: 2–4	£13 £27–£53	£173 £347–£693
Prestylon	460 mg EPA, 380 mg DHA (1 g)	Secondary prevention <3 months after MI or hypertriglyceridaemia	Following MI: 1 capsule Hypertriglyceridaemia: 2–4	£10 £20–£40	£130 £260–£520
Teromeg	460 mg EPA, 380 mg DHA (1 g)	Secondary prevention <3 months after MI or hypertriglyceridaemia	Following MI: 1 capsule Hypertriglyceridaemia: 2–4	£11 £21–£43	£139 £277–£555
Maxepa	170 mg EPA, 115 mg DHA (1 g)	Severe hypertriglyceridaemia only	10 capsules	£41	£535

Sources: NHS Drug Tariff, May 2014[1021]; British National Formulary, May 2014[717]; MIMS online, May 2014[626]
DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid

Appendix N: Research recommendations

N.1 Simplifying risk assessment

1. What is the effectiveness of age-alone and other routinely available risk factors compared to complex multi-factorial risk assessment to identify people at high risk of developing CVD.

Why this is important

Current risk assessment tools rely on a complex set of data derived from demographic, lifestyle, physiological and biochemical parameters. The principal determinant of CVD risk is age, and this may be sufficient to identify high-risk populations. However, focusing on age alone may result in people being missed who are at higher risk as a result of other factors that do not require access to intensive resources, such as smoking status, family history and deprivation. It is important therefore to assess the age against validated simplified and complex CVD risk tools in prediction of people at high risk.

Criteria for selecting high-priority research recommendations:

PICO question	What is the effectiveness of age-alone compared to simplified and complex multi-factorial risk assessment for the identification of people at high risk of developing cardiovascular disease (CVD)?
Importance to patients or the population	This would inform the decision about which risk calculation or identification systems to use in NHS practice.
Relevance to NICE guidance	The outcomes of this study could dramatically simplify the complex assessments that are currently performed.
Relevance to the NHS	Simplification of risk assessments could reduce the financial impact of health risk assessment on NHS resource (staff time, laboratory costs) and benefit patients by allowing potential access to comprehensive risk assessment tools through non-traditional NHS settings (electronic phone applications, websites).
National priorities	NHS Cardiovascular Disease Health Service Framework (2001)
Current evidence base	Data exists from UK epidemiological cohort studies of the prospective assessments of the quality of CVD risk assessment using both the Framingham (2001) and QRISK-2 tools. However despite the relevance of age and other routinely collected risk factors as dominant risk factors for CVD the only studies to have investigated their utility have used computer-based simulation. A validation of the age-alone approach using a prospective hard outcomes epidemiological dataset is required to confirm or rebut claims about its practical utility as a risk assessment tool. A similar approach could aslo be adopted for other routinely reported risk factors.
Equality	Equality addressed as age-alone or combined with easily accessible socio-economic variables would simplify the complex subsets of CVD risk assignment generated by QRISK which only partially capture ethnic diversity, and lifestyle variation.
Study design	This is a primary research question that can be answered using a large prospective epidemiological cohort dataset which records CVD outcomes. The outcomes would be comparison of patients correctly classified for prospective CVD outcomes by age alone or by validated risk assessment tool calculated CVD risk in a large epidemiological data set. Calibration, discrimination and net classification would be among appropriate outcomes.
Feasibility	The research can be easily carried out as cohorts exist, for example the CPRD database or the THIN cohort.
Other comments	This is a further analysis of existing datasets that have already compared the utility of Framingham and QRISK2 in the prospective identification of high-risk

	individuals for developing CVD.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline

N.2 Individual patient-based outcomes meta-analysis for statin therapy

2. What is the improvement in the cost-effectiveness metrics for statin therapy in reducing CVD that can be obtained when using a complete individual patient-based outcomes meta-analysis data set compared with using published outcomes data?

Why this is important

This guideline development process uses published summary data from trials in a meta-analysis to inform the clinical efficacy of statins. This use of aggregate data has limitations. The use of individual patient data would allow use of time to event statistics and allow investigation of interaction with baseline risk. Such an approach can be used to validate the current approach and would provide useful information on limitations of use of summary data.

Criteria for selecting high-priority research recommendations:

PICO question	Adults aged 18–95 at risk of developing CVD or with established CVD. Event reduction and cost-effectiveness modelling in published and individual patient-based data (IPD) sets. Comparison of outcomes, relative efficacy, cost effectiveness of statin-based intervention on CVD outcomes. Efficacy of published data meta-analysis compared with IPD datasets to differentiate detailed dose efficacy of statins, role of baseline LDL-C in risk modification, validity of relative risk reduction assumptions and validation of potential novel risk calculation system.
Importance to patients or the population	This would inform the decision about which risk calculation or identification system and the optimal dose of statin to use in NHS practice.
Relevance to NICE guidance	The outcomes of this study could dramatically simplify the recommendations made for lipid-lowering therapy by identifying the optimal strategy to use to reduce CVD risk. It would inform the optimum health economic models to be used by NICE in the assessment of interventions. It could validate a new CVD risk assessment system.
Relevance to the NHS	The outcomes of this research could revise or simplify the strategy to be used for treatment of patients with CVD or at high risk of developing CVD.
National priorities	NHS Cardiovascular Disease Health Service Framework (2001).
Current evidence base	All health economic assessments to date have relied on published study-level outcomes and none have had access to IPD baseline and outcome data. A number of meta-analyses have investigated the efficacy of statins on LDL-C and CVD outcomes. The outputs of these analyses may or may not remove the heterogeneity associated with statin therapy for both reductions in LDL-C and CVD outcomes. An IPD comprehensive modelling approach would allow the validity of the assumptions made in current modelling and in the outputs of the meta-analyses to be rigorously tested. These may redefine the hierarchy of data sets to be used in future NICE appraisals.
Equality	IPD allows this to systemically addressed while only approximations and sensitivity analyses can be derived from aggregated data.
Study design	This is a primary research question that can be answered using a large prospective IPD dataset which records CVD outcomes from numerous statin

	outcome studies.
Feasibility	The individual-patient based baseline and outcome data set exist as part of the Cholesterol Treatment Trialists Collaboration.
Other comments	This is a unique opportunity to validate and attempt to improve models of the efficacy of lipid-lowering drug therapy
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

N.3 Statin therapy in older people

3. What is the effectiveness of statin therapy in older people?

Why this is important

The UK population is ageing and atherosclerosis is an age-associated process. Few trials assessing cardiovascular outcomes have recruited many people aged over 80 years yet the important effect of age on CVD risk suggests that all patients in this group should be offered statin therapy. However there is no evidence to validate the CVD benefits and side effects of statin therapy in this age group. Controversy also exists about the efficacy of statins in preventing or promoting other chronic diseases of ageing such as dementia, Parkinson's disease, or age-related macular degeneration.

Criteria for selecting high-priority research recommendations:

PICO question	What is the effectiveness of statin therapy in older people?
Importance to patients or the population	This would inform the decision about whether statin treatment is beneficial in the elderly (aged over 80 years) who have not had a previous CVD event
Relevance to NICE guidance	The outcomes of this study could dramatically simplify the recommendations made for lipid-lowering therapy and prevent over- or under-treatment of the elderly.
Relevance to the NHS	The outcomes of this research could revise or simplify the strategy to be used for treatment of elderly patients at high risk of developing CVD.
National priorities	NHS Cardiovascular Disease Health Service Framework (2001).
Current evidence base	Most statin trials have limited their recruitment to under age 75 years. A small number of more elderly patients have been included in some trials (for example, PROSPER) or been recruited with wider age entry criteria (for example, HPS). Uncertainty remains about the benefits of lipid-lowering in the elderly and especially about the effects of statins on non-atherosclerotic diseases of the elderly. The trial is analogous in concept to HYVET, which investigated and changed practice when it identified the increased efficacy of antihypertensive therapy in the elderly compared to middle-aged groups.
Equality	This trial addresses equality issues as women have longer survival than men and would be most disadvantaged by age-based over-treatment by age-alone.
Study design	This is a primary research question that can be answered by a randomised controlled outcomes trial. The population would be adults aged over 80 years without clinical evidence of CVD. The intervention would be statin treatment compared with placebo or usual care. Suggested outcomes are: (1) primary outcomes: CVD death, fatal and non-fatal myocardial infarction and stroke (2) secondary outcomes: rates of revascularisation, angina, PAD

	(3) tertiary outcomes: risks of developing non-atherosclerotic diseases potentially affected by statin therapy, for example dementia, Parkinson's disease, age-related macular degeneration, chronic renal disease, prostate and other cancers. Adverse events to be measured would be myalgia, rates of diabetes, adherence.
Feasibility	This study is feasible as the smaller PROSPER study was performed in Scotland in the 70–80 year age group and the over 80 year age group is a rapidly increasing proportion of the population. A multi-national study may also be feasible given the topicality of this question.
Other comments	This trial would fill a major gap in the evidence for lipid-lowering therapies.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.4 Lipid modification therapy in people with type 1 diabetes

4. What is the effectiveness of statins or other LDL cholesterol-lowering treatment in patients with type 1 diabetes?

Why this is important

Patients with type 1 diabetes have increased CVD risk derived from age, gender, glycaemia, blood pressure, renal function and lipid levels as identified in epidemiological studies. No trial has investigated the efficacy of statin therapy or other LDL cholesterol lowering therapies in people with type 1 diabetes.

Criteria for selecting high-priority research recommendations:

PICO question	What is the effectiveness of statin treatment in patients with type 1 diabetes?
Importance to patients or the population	This would inform the decision about whether high intensity statin (LDL-C lowering) treatment is beneficial in patients with type 1 diabetes compared to usual care.
Relevance to NICE guidance	The outcomes of this study could define the treatment recommendations made for lipid-lowering therapy in patients with type 1 diabetes
Relevance to the NHS	The outcomes of this research could revise the strategy to be used for treatment of lipid levels in patients with type 1 diabetes.
National priorities	NHS Cardiovascular Disease Health Service Framework (2001). NHS Diabetes Health Service Framework (2013).
Current evidence base	Epidemiological studies (for example, DCCT) show that patients with type 1 diabetes are at high risk of CVD. This is related to demographic variables, blood pressure, renal function and glycaemic control as well as lipid levels. While being at high risk, patients with type 1 diabetes have superficially 'normal' lipid profiles which may actually be composed of dysfunctional lipid particles. Most statin trials have not recruited patients with type 1 diabetes. The only data relate to 600 patients with type 1 diabetes aged over 40 years recruited to HPS where no heterogeneity was found in outcomes compared with patients with type 2 diabetes and the general CVD risk population. Type 1 diabetes can be diagnosed at a young age and important questions exist as to when statins should be initiated and at what dose.
Equality	This trial would address equality issues in a population susceptible to early-onset autoimmune disease and has potential relevance for the treatment of children and adolescents.
Study design	This is a primary research question that can be answered by a randomised

	controlled trial. The population would be adults with type 1 diabetes. The intervention would be high intensity statin and/or additional LDL-C treatment compared with usual care. Comparison of CVD outcomes, diabetes-specific microvascular end points (for example, progression of renal or eye disease) and side-effects of treatment. Primary outcomes: CVD death, fatal and non-fatal myocardial infarction and stroke. Secondary outcomes: rates of revascularisation, angina, PAD. Tertiary outcomes: individual components of the primary end point; risks of developing non-atherosclerotic diseases potentially affected by statin therapy, for example, progression of renal disease, eye disease.
Feasibility	This study is feasible as registers exist of patients with type 1 diabetes which would allow for the recruitment of adults with type 1 diabetes who would be necessary to power the CVD outcomes. Type 1 diabetes is increasing in frequency and its epidemiology is changing given longer survival due to improved glycaemic control (insulin therapy) but at the expense of a rapid increase in secondary risks due to increased prevalence of obesity and the metabolic syndrome.
Other comments	This trial would fill a major gap in the evidence for lipid-lowering therapies.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.5 Comparative effectiveness and risks of alternative doses of atorvastatin

5. What is the clinical effectiveness and rate of adverse events of statin therapy using atorvastatin 20 mg per day compared with atorvastatin 40 mg per day and atorvastatin 80 mg per day in adults without established CVD?

Why this is important

This guideline has established that atorvastatin 20 mg is clinically and cost effective for the primary prevention of CVD and should be recommended for those at 10% risk of cardiovascular events as assessed using the QRISK2 calculator. However, this analysis looked at the effectiveness of treatment shown by 'high-intensity' statins as a group, as it was not possible to establish the relative effectiveness of atorvastatin 20 mg, 40 mg and 80 mg. If atorvastatin 40 mg or 80 mg are more clinically effective in reducing cardiovascular events then the use of either could be cost effective compared to atorvastatin 20 mg. The rates of adverse events resulting from different doses of atorvastatin in routine clinical practice are also uncertain and would need to be considered in combination with effectiveness in assessing the relative costs and benefits of different doses of atorvastatin.

Criteria for selecting high-priority research recommendations:

PICO question	What is the clinical effectiveness and rate of adverse events of statin therapy using atorvastatin 20 mg per day compared with atorvastatin 40 mg per day and atorvastatin 80 mg per day in adults without established CVD?
Importance to patients or the population	If atorvastatin 40 mg or 80 mg are substantially more effective in reducing clinical end points compared to atorvastatin 20 mg in primary prevention, but without a significant increase in adverse events, people could be recommended to routinely initiate treatment with atorvastatin 40 mg or 80 mg and would receive greater health benefits.

Relevance to NICE guidance	The outcomes of this study would inform an updating of the economic modelling carried out in this guideline, and if cost effective this could change the standard treatment recommended for primary prevention from atorvastatin 20 mg to atorvastatin 40 mg or 80 mg.
Relevance to the NHS	Changing the standard recommended treatment would reduce the need to assess people taking primary prevention treatment to consider if it is appropriate to increase their dose, but would otherwise have little impact on the total number of GP consultations. No change would be required in the organisation or delivery of risk assessment or follow-up. Atorvastatin 40 mg and 80 mg are more expensive drugs, but would only be recommended if they were cost effective due to their effect in reducing future cardiovascular events and hence future healthcare costs.
National priorities	NHS Cardiovascular Disease Health Service Framework (2001)
Current evidence base	The analysis in this guideline looked at the effectiveness of 'high-intensity' statins as a class, as there was insufficient evidence to compare the effectiveness of high-intensity statins against each other. The high-intensity class included 3 different doses of atorvastatin, as well as simvastatin 80 mg per day which is not recommended due to its increased rate of myopathy, and 3 doses of rosuvastatin which are all considerably more expensive than atorvastatin. These different doses of atorvastatin differ in their ability to reduce levels of LDL and total cholesterol[819] and are thought to differ in their ability to reduce cardiovascular events, including death. However, we identified no randomised clinical trials meeting our inclusion criteria that compared any 2, or all 3, of atorvastatin 20 mg, 40 mg and 80 mg against each other; we identified only 1 trial comparing atorvastatin 20 mg with placebo, and no trials comparing atorvastatin 40 mg with placebo. In addition, the rates of adverse events caused by statins were an important consideration in this guideline, particularly reported myalgia leading to discontinuation of statins or the need to change to an alternative statin or dose. It is known that some adverse events can increase with increasing dose of statin – this is the case for myopathy in simvastatin. The comparative rates of adverse events between atorvastatin 20 mg, 40 mg and 80 mg are not clear, due to the lack of trials already stated.
Equality	Current trial data is under-representative of some groups of the population, including women, older people, and those with comorbidities. A large scale pragmatic trial carried out in UK primary care could include all subgroups as commonly as they are found in the population. For large enough subgroups outcomes could be compared to look for differences in effectiveness or adverse events related to subgroups.
Study design	A proposal has been put forward by van Staa and colleagues at the Clinical Practice Research Datalink to carry out pragmatic randomised controlled trials using routine electronic health records.[1375] Such trials would be large scale but low cost by recruiting patients in GP surgeries and following them by using the electronic health records generated by their GPs in the course of normal treatment and assessment. In the case of statins, this would require recruiting patients at the point following risk assessment when the person and their GP have agreed that statins should be initiated, so that the choice of which dose of atorvastatin to prescribe is randomised.
Feasibility	The research can be carried out using the existing CPRD UK primary care cohort. This would mean that the population eligible for the trial would naturally represent the UK population of interest. A pilot trial (RETRO-PRO, ISRCTN33113202) is currently being undertaken by CPRD researchers, comparing simvastatin with atorvastatin, but the same approach could be used to compare different doses of atorvastatin.
Other comments	The implementation of the recommendations in this guideline, which

	recommend treatment for a wider group of people for primary prevention than previously, provides an opportunity to carry out this research on a large cohort of people who will be initiating statin treatment for the first time.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline

Appendix O: How this clinical guideline was updated

O.1 Amended recommendation wording (change to meaning)

The evidence has not been reviewed but changes have been made to the recommendation wording that change the meaning. These changes are marked with yellow shading below.

Recommendation in 2008 guideline	Recommendation in current guideline	Reason for change
1.1.1 For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged 40–74 who are likely to be at high risk.	1.1.1 For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]	The tools available for estimating CVD risk in 2008 had an upper age range of 74 years. QRISK2 has an upper age range of 84 years. The age range was therefore removed for clarity.
1.1.4 People should be prioritised for a full formal risk assessment if their estimated 10-year risk of CVD is 20% or more.	1.1.4 Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]	The threshold for treatment has been changed from 20% to 10% because of new health economics results.
1.1.10 Risk equations should not be used for people with pre-existing: CHD or angina stroke or transient ischaemic attack peripheral vascular disease.	1.1.15 Do not use a risk assessment tool for people with pre-existing CVD. [2008, amended 2014]	The GDG made this recommendation more general to include all CV diseases.
1.1.11 Risk equations should not be used for people who are already considered at high risk of CVD because of: familial hypercholesterolaemia or other monogenic disorders of lipid metabolism diabetes, see 'Type 2 diabetes: the management of type 2 diabetes (update)' (NICE clinical guideline 66).	1.1.16 Do not use a risk assessment tool for people who are at high risk of developing CVD because of familial hypercholesterolaemia (see Familial hypercholesterolaemia [NICE clinical guideline 71]) or other inherited disorders of lipid metabolism. [2008, amended 2014]	The bullet point about type 2 diabetes has been deleted because the GDG made separate specific recommendations for this subgroup.
1.1.13 When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold of 20%, healthcare professionals should consider other factors that: may predispose the person to premature CVD, and may not be included in calculated risk scores.	1.1.17 When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold for treatment, take into account other factors that: may predispose the person to premature CVD and may not be included in calculated risk scores. [2008, amended 2014]	The threshold for treatment has been changed because of new health economics results. 'healthcare professionals should consider' has been amended to: 'take into account' in line with current NICE style for recommendations in clinical guidelines.
1.1.20 CVD risk may be	1.1.19 Recognise that CVD risk will be	

Recommendation in 2008 guideline	Recommendation in current guideline	Reason for change
underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Clinical judgement should be used to decide on further treatment of risk factors in people who are below the 20% CVD risk threshold.	underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the CVD risk threshold for treatment. [2008, amended 2014]	The threshold for treatment has been changed because of new health economics results.
1.1.21 CVD risk scores may not be appropriate as a way of assessing risk in people who are at increased CVD risk because of underlying medical conditions or treatments. These include people treated for HIV or with antipsychotic medication, people with chronic kidney disease and people with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.	1.1.18 Recognise that standard CVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include: people treated for HIV people with serious mental health problems people taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs people with autoimmune disorders such as systemic lupus erythematosus and other systemic inflammatory disorders. [2008, amended 2014]	The list of underlying medical conditions had been updated.
1.1.22 People aged 75 or older should be considered at increased risk of CVD, particularly people who smoke or have raised blood pressure. They are likely to benefit from statin treatment. Assessment and treatment should be guided by the benefits and risks of treatment, informed preference and comorbidities that may make treatment inappropriate.	1.1.21 Consider people aged 85 or older to be at increased risk of CVD because of age alone, particularly people who smoke or have raised blood pressure. [2008, amended 2014]	'should be considered' has been amended to: 'consider' in line with current NICE style for recommendations in clinical guidelines. The age value has been changed to 85, as this is the upper limit of the QRISK2 assessment tools. The part on treatment has been deleted, as recommendations on treatment are listed in section 1.3.
1.2.5 In order to encourage the person to participate in reducing their CVD risk, the healthcare professional should: find out what, if anything, the person has already been told about their CVD risk and how they feel about it explore the person's beliefs about what determines future health (this	1.1.27 To encourage the person to participate in reducing their CVD risk: find out what, if anything, the person has already been told about their CVD risk and how they feel about it explore the person's beliefs about what determines future health (this may affect their attitude to changing risk)	The words 'long-term' have been added to the third bullet in relation to medication to emphasise the need to discuss people's views about taking medication long term.

Recommendation in 2008 guideline	Recommendation in current guideline	Reason for change
may affect their attitude to changing risk) assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take medication assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication inform them of potential future management based on current evidence and best practice involve them in developing a shared management plan check with them that they have understood what has been discussed.	assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take long-term medication assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication inform them of potential future management based on current evidence and best practice involve them in developing a shared management plan check with them that they have understood what has been discussed. [2008, amended 2014]	
1.2.7 If the person's CVD risk is considered to be at a level that merits intervention but they decline the offer of treatment, they should be advised that their CVD risk should be considered again in the future.	1.1.28 If the person's CVD risk is at a level where intervention is recommended but they decline the offer of treatment, advise them that their CVD risk should be reassessed again in the future. Record their choice in their medical notes. [2008, amended 2014]	The GDG considered it important that people's involvement in decision-making and their choices are adequately recorded.
1.3.7 People at high risk of CVD or with CVD should be advised to take 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population. (see Physical activity guidelines for adults) [2008,]	1.2.7 Advise people at high risk of or with CVD to do the following every week: at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). [2008, amended 2014]	This recommendation has been updated because the chief medical officer issued changes to recommendations on physical activity in 2011.
1.3.8 People who are unable to perform moderate-intensity physical activity at least 5 days a week because of co-morbidity, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity. [2008]	1.2.9 Encourage people who are unable to perform moderate-intensity physical activity because of comorbidity, medical conditions or personal circumstances to exercise at their maximum safe capacity. [2008, amended 2014]	This recommendation has been updated because the chief medical officer issued changes to recommendations on physical activity in 2011.
1.4.18 If a person has acute coronary syndrome, statin treatment should not be delayed until lipid levels are available. A fasting lipid sample should be taken about 3 months after the start of treatment.	1.3.22 If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment. [2008, amended 2014]	The GDG considered that a fasting sample is not necessary if non-HDL cholesterol is measured (see recommendation 1.3.4). The GDG wished to

Recommendation in 2008 guideline	Recommendation in current guideline	Reason for change
		highlight the importance of taking a lipid sample also on admission.

Appendix P: NICE Technical Team

Name	Role
Sarah Willett	Guideline Lead
Phil Alderson	Clinical Adviser
Caroline Keir	Guideline Commissioning Manager
Margaret Ghlaimi	Guideline Coordinator
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Appendix Q: Deleted parts from CG67 (2008)

Preface

As a practising GP, I know just how important it is to prevent cardiovascular disease. Seeing a young patient in the prime of their life suddenly struck by a vascular event is devastating. Sadly this is something that still occurs all too frequently. From talking to many GPs and nurses it has become clear that there is considerable uncertainty about which patients to target for preventative treatment, how to respond to a request for lipid measurement and the thresholds at which to initiate treatment. As a result there is considerable variation in practice and in outcomes. So I really welcome this guideline which brings much needed clarity for clinicians who have to manage patients with risk factors for heart disease every day.

It is particularly timely as there considerably interest from the public in staying healthy. Indeed the NHS is being reshaped to focus much more on health rather than disease and is introducing initiatives in vascular disease screening. This is right because cardiovascular disease is a major cause of disability and death in the United Kingdom. In particular it is the most common cause of premature death. We now know much about the epidemiology of cardiovascular disease, risk factors for its development and have available interventions that reduce morbidity and mortality. The risk of a future CVD event can be calculated from these risk factors and people at highest risk can be identified.

Although this guideline is relevant to all settings, it emphasizes the important role of primary care. The guideline promotes the adoption of a systematic strategy in primary care to identify those at risk and to offer to them the benefit of lifestyle advice and preventative care. The emphasis is on treating patients according to their overall level of risk rather than treating cholesterol levels in isolation. The use of the general practice electronic patient record and the routine data collected there allows practitioners to search for and offer treatment to those patients in their community who are at highest risk.

The guideline rightly emphasises the requirement for a partnership with patients and the importance of patient understanding of concepts of risk and preventative care. Communication with patients remains important in relation to drug treatment. As well as recommendations in regard to identifying patients at risk, there is guidance on the use of lipid lowering drugs in primary prevention and for those patients who have already had a cardiovascular event. Happily this is not considered in isolation but in the context of appropriate lifestyle advice.

I commend this guideline to clinicians and healthcare organisations and urge them to implement it as widely as possible: I know that I will use on a daily basis in clinical practice.

Professor Mayur Lakhani CBE FRCP FRCPE FRCGP

GP and Immediate Past Chairman of the Royal College of General Practitioners

Medical Director, NHS East Midlands

Key priorities for implementation

- For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged between 40 and 74 who are likely to be at high risk.

- People should be prioritised on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.

- Risk equations should be used to assess CVD risk.

- People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

o presents individualised risk and benefit scenarios

o presents the absolute risk of events numerically

o uses appropriate diagrams and text.

(See www.npci.org.uk)

- Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

o smoking status

o alcohol consumption

o blood pressure (see 'Hypertension', NICE clinical guideline 34)

o body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)

o fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)

o fasting blood glucose

o renal function

o liver function (transaminases)

o thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).

- Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

Secondary prevention of CVD

- For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comordbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

  - smoking status
  - alcohol consumption
  - blood pressure (see 'Hypertension', NICE clinical guideline 34)
  - body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
  - fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
  - fasting blood glucose
  - renal function
  - liver function (transaminases)
  - thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

- Statin therapy is recommended for adults with clinical evidence of CVD.

- People with acute coronary syndrome should be treated with a higher intensity statin. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.

- Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

- In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin8 should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

Q.1 Introduction

Q.1.1 Background

Cardiovascular disease (CVD), which comprises coronary heart disease (CHD) and stroke, is the main cause of death in England and Wales. There are more than 3 million people living with CVD. In 2005, CVD was the cause of one in three deaths, accounting for 124 000 deaths; 39 000 of those who died were younger than 75 years of age. For every one fatality, there are at least two people who have a major non-fatal cardiovascular event. There are over 3 million people living with coronary heart disease or stroke.

This epidemic has been socially generated by smoking, diets high in saturated fats and salt and a sedentary lifestyle. The epidemic peaked in the 1970s and 1980s and death rates have halved since then. Despite this reduction CVD remains a leading cause of death, in particular of premature death,

an increasing cause of morbidity and a major cause of disability and ill-health. The UK CVD death rates continue to exceed those of its European neighbours. It is estimated that 60% of the CVD mortality decline in the UK during the 1980s and 1990s was attributable to reductions in major risk factors, principally smoking. Treatment of individuals, including secondary prevention, accounts for the remaining 40% of the decline in mortality.[1362]

In spite of evidence that mortality from CVD is falling, morbidity appears to be rising. CVD has significant cost implications and was estimated to cost the NHS almost £14750 million in 2003 and the economy around £30 billion a year.

Age is the main determinant of CVD which predominantly affects people over 50 years. Men under 75 years are three times more likely than women to die from CVD. Apart from age and sex, three modifiable risk factors, smoking, raised blood pressure and cholesterol make the major contribution to CVD incidence, particularly in combination. They account for 80% of all premature coronary heart disease.[464] There are in addition identifiable population groups who may be at particular risk and could be targeted for treatment. CVD is strongly associated with low income and social deprivation and shows a North-South divide in both the UK and Europe as a whole. Despite the male propensity to CVD, the lifetime burden is greater in women because of their longevity and their increased risk of stroke over the age of 75 years.[1230] Women have a higher case-fatality rate, are more likely to be under-diagnosed and less likely to be optimally treated. Women in low income groups are the exception to the trend of reducing mortality from CVD over the past 20 years. South Asian men are more likely to develop CVD at a younger age. Family history of premature coronary heart disease identifies an important group which contains those people with a genetic pre-disposition.

Q.2 Management

Strategies for the prevention of CVD are threefold. First are interventions to reduce the prevalence of CVD risk factors in the general population. The largest number of CVD events will occur in those at low risk. Smoking cessation combined with changes in mean blood pressure and cholesterol through national reductions in salt intake, saturated fat consumption and increases in physical activity are fundamental to the national strategy for improvement.

The second strategy is interventions in individual people at high risk of developing CVD and focusing health service resources on those at greatest risk with most to gain. This strategy, largely based in primary care, includes smoking cessation and the identification and assessment of those at high risk with appropriate advice on diet, physical activity and treatment for high blood pressure and lipid modification. The NSF for CHD in England and Wales advocates both approaches. For primary prevention, the NICE technology appraisal, 'Statins for the prevention of cardiovascular events' (TA 94, 2007) recommends that the current National Service Framework threshold for statin treatment (30% CHD ten-year risk, equivalent to a 40% CVD risk) be reduced by half, to a 20% CVD ten-year risk. In addition to those people who are already known to have diabetes or CVD, the adoption of this new threshold will identify 5 million more people as potential candidates for treatment depending on which risk score is used.[651]

The third strategy is for secondary prevention in people with established cardiovascular disease which includes modification of lipids. Serum cholesterol often remains at unacceptably high levels[267] and can be further improved with advice, support and treatment. Treatment for high blood pressure and other preventive treatment may also be sub-optimal.[480]

Trials of statin therapy have demonstrated that lowering LDL cholesterol by 1 mmol/l reduces CVD events by 21% and total mortality by 12%, irrespective of baseline risk. Although there have been major improvements in the use of statins for secondary prevention there is still substantial variation in their use by clinicians. Wider and improved use of statins would have a major public health impact.

Adherence to treatment is poor even among those who have experienced a CVD event and non-adherence is associated with worse outcomes.[680,1136,1419]

For primary prevention, adherence to treatment is an even greater challenge than for those who have had a major event. Convincing people who feel well, that they need lifestyle change or lifelong drug treatment requires high quality information and communication.

The scope for this guideline was limited to the identification and assessment of CVD risk and to the assessment and modification of lipids in people at risk of CVD or people with known cardiovascular disease. The guideline development group wishes to make it clear that lipid modification should take place as part of a programme of risk reduction and also include attention to the management of all other known risk factors.

Q.3 Aim of the guideline

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'.[341]

This guideline gives recommendations to clinicians and other groups listed in 2.5.1, about lifestyle modification, drug therapy, patient information and the communication of patient risk assessment and information surrounding lipid modification for primary and secondary prevention of CVD.

Q.4 How the guideline is set out

The recommendations for all the topics in each clinical chapter are listed at the start of the chapter. Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. The evidence extraction reports that describe the studies reviewed are found in Appendices D and E.

Q.5 Scope

The guideline was developed in accordance with a scope given by NICE. The scope set the remit of the guideline and specified those aspects of lipid modification to be included and excluded. The scope was published in August 2005 and is reproduced in Appendix B.

Q.5.1 Who the guideline is intended for

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales. This includes:

healthcare professionals who work within the primary, community, community pharmacy and hospital secondary care settings.

those with responsibilities for commissioning and planning health services such as primary care trust commissioners, Welsh Assembly government officers

public health and trust managers

people (aged 18 years and older) with CVD or without established CVD but who are at high risk of developing CVD due to a combination of cardiovascular risk factors including raised blood pressure and hypertension, and/or who are overweight or obese.

Q.5.2 Areas outside the remit of the guideline

The guideline does not cover people:

a) with familial hypercholesterolaemia and familial hypertriglyceridaemia (familial lipoprotein lipase deficiency; familial apolipoprotein C-II deficiency)

b) with type 1 and type 2 diabetes

c) with familial clotting disorders and/or other defined genetic disorders that increase cardiovascular risk

d) who are at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes or as a result of drug treatment

e) The scope was altered in December 2006 to encompass use of statins post MI.

The statement of explanation from the NICE website is 'The Institute is currently preparing clinical guidelines on 'MI: Secondary Prevention' (scheduled publication March 2007), and on 'Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' (scheduled publication December 2007). The guidelines have been developed alongside the technology appraisal advice on Statins for the prevention of cardiovascular events (published January 2006), and also Ezetimibe for the treatment of hypercholesterolemia (scheduled publication August 2007).

The scope for the MI Secondary Prevention states that it will provide advice on "lipid modifying drugs with specific reference to the additional advice for patients post MI and incorporating the statins technology appraisal and cross referencing to the hyperlipidaemia guideline".

In the light of the more detailed recommendations being developed in the Lipids Modification guideline, the Institute has agreed the most appropriate way forward is for the MI guideline to confine its recommendations to those in the technology appraisal on Statins, and does not include recommendations on dosage or cholesterol monitoring etc. The Lipids guideline will then take on responsibility for making recommendations regarding statin doses and targets, and include recommendations for patients following an MI.'

This guideline also does not cover:

1 the identification, assessment and management of people with pre-diabetes/metabolic syndrome.

2 the clinical management of conditions considered to be risk factors for CVD, including raised blood pressure/hypertension, smoking, obesity, and blood clotting abnormalities.

3 self-medication of individuals with lipid-regulating drugs, specifically use of over-the-counter drugs, including statins.

4 the clinical management of people with lipid disorders considered to merit referral to secondary care for specialist assessment and follow-up.

5 the clinical management of people with CHD (angina), stroke and peripheral arterial disease except as it relates to lipid modification in the context of secondary prevention.

Q.6 Responsibility and support for guideline development

Q.6.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to NICE, and is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres that focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the NCC-PC's host organisation. The Royal Pharmaceutical Society and the Community Practitioners' and Health Visitors' Association are partner members with representation of other professional and lay bodies on the Board. The RCGP holds the contract with NICE for the NCC-PC. The work has been carried out on two sites in London, where the work on this particular guideline was based, and in Leicester under contract to the University of Leicester.

Q.6.2 The Development Team

The Development Team had the responsibility for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

Guideline Lead, who is a senior member of the NCC-PC team and has overall responsibility for the guideline.

Information Scientist, who searched the bibliographic databases for evidence to answer the questions posed by the GDG.

Reviewer (Senior Health Services Research Fellow), with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG.

Health Economist, who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness.

Project Manager, who was responsible for organising and planning the development, for meetings and minutes and for liaising between NICE and external bodies.

Clinical Adviser, with an academic understanding of the research in the area and its practical implications for the healthcare service, who advised the Development Team on searches and interpretation of the literature.

With the exception of the Clinical Adviser, all of the Development Team was based at the NCC-PC. Applications were invited for the post of Clinical Adviser, who was recruited to work on average one half-day per week on the guideline. The members of the Development Team attended the GDG meetings and participated in them.

For this guideline, the Clinical Adviser also took the role of Chair for the GDG meetings.

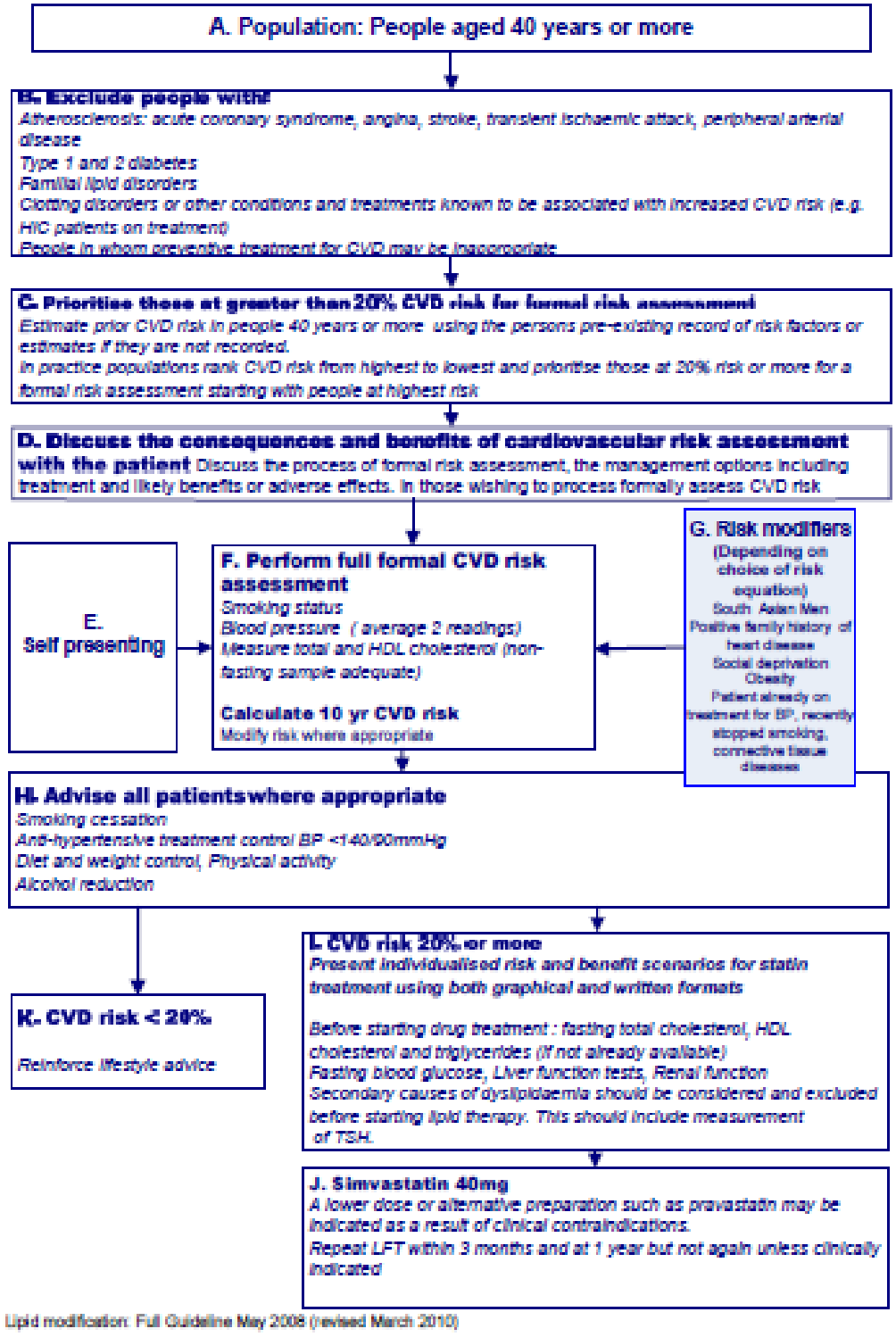
- **Guideline Development Group Meetings**

The GDG met at 4- to 5- week intervals for 18 months to review the evidence identified by the Development Team, to comment on its quality and relevance and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG, which met following the consultation to review and agree any changes to the guideline resulting from stakeholder comments

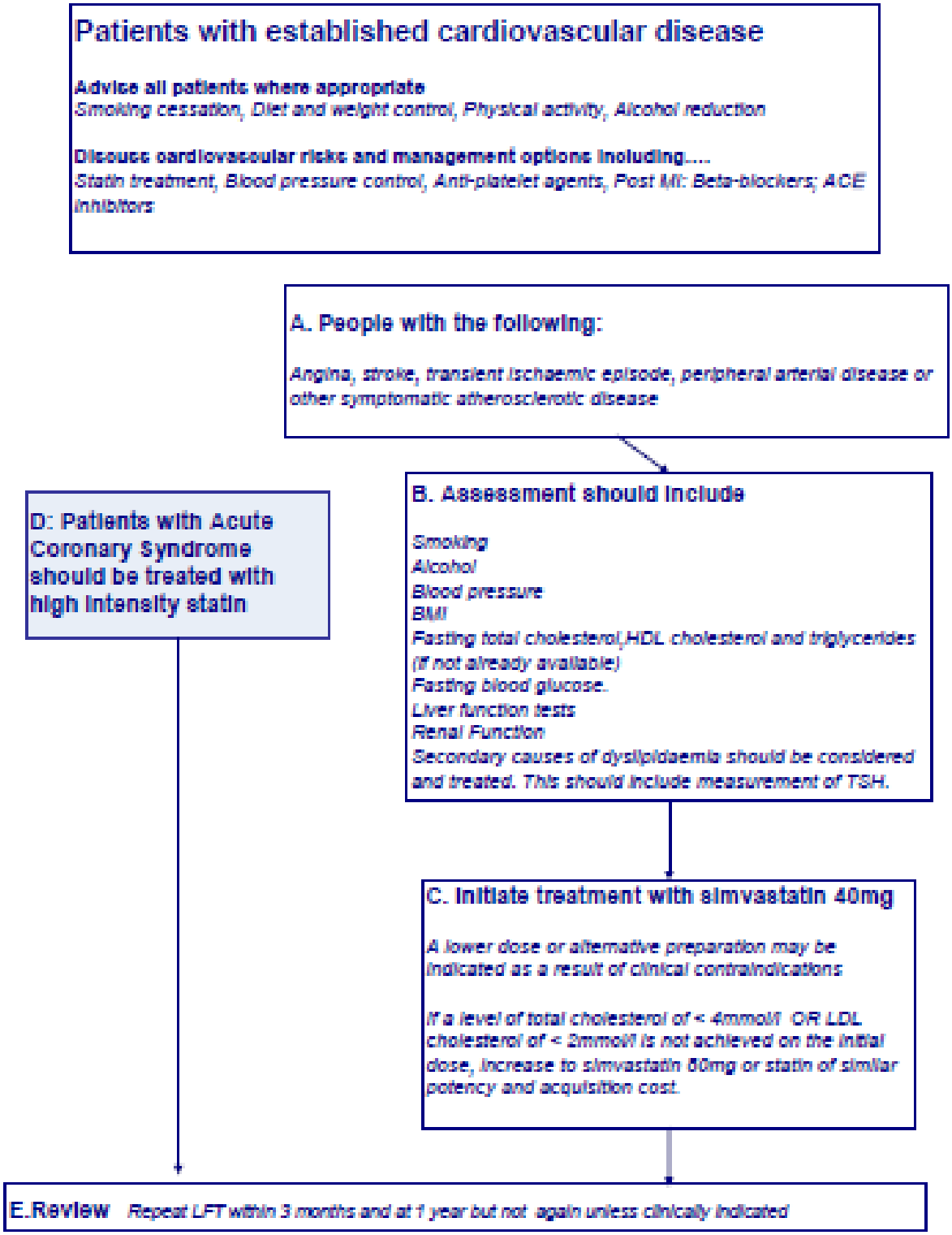
Q.7 Care pathways

Two clinical care pathways have been designed to indicate the essential components of lipid modification for the primary and secondary prevention of CVD.

Primary prevention care pathway



– **Secondary prevention care pathway**



Q.8 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

Q.8.1 Risk estimation methods

How can CVD risk be best estimated in the population of England and Wales to identify people at high risk of developing CVD for lipid modification therapy?

Why this is important

Current risk estimation is based upon the American Framingham equations which are limited for use in the UK by their development in a historic American population. The Framingham equations overestimate risk by up to 50% in contemporary northern European populations, particularly people living in more affluent areas. They underestimate risk in higher risk populations, such as those that are most socially deprived. Framingham makes no allowance for family history of premature CHD and does not take account of ethnicity, but does have a full dataset. Two new risk scores have recently been developed in the UK. ASSIGN was developed using a Scottish cohort and QRISK using data from UK general practice databases. These scores have the advantage of including other variables such as measures of social deprivation and family history. There is an urgent need to establish which score is most acceptable for use in the population of England and Wales. NICE should review the relevant recommendations relating to risk assessment as soon as sufficient new data are available to address this.

Research is required:

to adjust Framingham for use in the UK population, to assess the use of ASSIGN in UK populations outside Scotland, to validate QRISK in independent and clinical datasets and to assess the performance of the scores against each other

to assess the feasibility of using scores with an increased number of variables, such as social deprivation, in routine clinical practice, particularly in community and secondary care settings where access to patient electronic records and computers is less likely to be available

to assess the added value of including variables such as ethnicity, alcohol intake and chronic kidney disease to risk assessment scores.

Q.8.2 Plant sterols and stanols

What is the effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event?

Why this is important

Some people at increased risk of CVD might avoid the need to use drugs to modify their cholesterol levels if they make sufficient changes to their diet. Plant sterols and stanols have been shown to reduce cholesterol levels, but it is not known whether the consumption of plant sterols as part of a low-fat diet will provide worthwhile additional benefit and whether they reduce CVD events.

There is a need for trials to test both efficacy and effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event. These trials should test whether plant sterols or stanols change lipid profiles and reduce CVD events under best possible conditions. Randomised controlled trials are needed to test the effectiveness of advising people who are at high risk of experiencing a first CVD event to include food items containing plant sterols or stanols in a low fat diet. The trial should last for at least 2 years and should consider appropriate outcomes.

Q.8.3 Communication of CVD risk

How is CVD risk most effectively communicated to patients? What methods are best and how do these differ for particular groups, such as older people or members of minority ethnic groups?

Why this is important

The methods of risk communication (both the content and means of delivery) should be guided by current evidence. Controlled trials should be conducted comparing the impact of different methods of risk communication and decision aids on patient comprehension, the patient experience of decision-making and actual treatment decisions taken by patients. The aim should be to generate evidence to support the improvement of risk communication and patient decision-making. The content should include absolute rather than relative risks. Numerical data should be presented in both words and numbers, and visual and graphical aids should be used. Such studies might consider a number of delivery mechanisms, including advice from a clinician, a trained 'coach', self-accessed educational presentations via computer or DVDs, peer or lay advisers, and other appropriate means. Trials should also investigate the preferences and views of people from different ethnic groups and of different ages and sex.

Q.8.4 Impact of decision aids

What is the impact of using clinical decision aids that include an assessment of absolute risk to prioritise the prescription of risk-reducing treatment for the primary prevention of CVD?

Why this is important

Risk scoring methods are recommended to help target preventive treatment at people who are asymptomatic but at high risk of CVD. As with any health technology, risk scoring methods should be shown to favourably influence individual people's health outcomes or risk factors, if they are to be used in primary prevention strategies.

There are no studies involving risk scoring methods in general community populations. Importantly, there is no evidence to support the use of computer-based clinical decision support systems in the primary prevention of CVD.

Being offered long-term primary prevention treatment, or not, is highly significant for individuals, and because of the large numbers of people involved, the medical, financial and social implications for society are considerable. Although the use of clinical decision aids incorporating CVD risk assessment has intuitive appeal and is encouraged in guidelines, the components of an effective decision aid and its impact on individuals remain almost completely unknown.

Outcomes should include morbidity, individual absolute risk, adverse effects, changes in risk behaviours such as smoking, changes in treatment, and a qualitative assessment of the views of both the clinicians using the decision aids and the people being prioritised to either receive preventive treatment or not.

Q.8.5 Treating to target

What is the clinical and cost effectiveness of incremental lipid lowering with HMG CoA reductase inhibitors (statins) and/or ezetimibe to reduce CVD events: (i) in people without established CVD disease who have a 20% or greater risk of CVD events over 10 years; (ii) in people with established CVD?

Why this is important

Several studies with CVD outcomes were identified during the development of this guideline that randomised participants to specific doses of statins to assess the additional effect of higher intensity statins versus lower intensity statins. The incremental cost effectiveness (including adverse events) of these drugs (either alone or in combination with other classes of drug) to reduce CVD events by

treating to target levels of total cholesterol of either 5 mmol/litre or 4 mmol/litre (or comparable LDL cholesterol levels) is unknown.

Q.8.6 Vascular dementia

Does lowering cholesterol with statins reduce cognitive decline and dementia in patients with prior stroke and other vascular events?

Why is this important?

People who have had a stroke are at a very increased risk of losing the ability to think and remember things ('cognitive decline') and of developing dementia. Approximately half of dementia is related to poor circulation in the brain ('vascular dementia'). Statins reduce blood cholesterol levels and the development of narrow blood vessels, and vascular events including stroke and myocardial infarction. However, it is not known whether statins reduce cognitive decline and vascular dementia. There is a need for trials to test the efficacy of statins on cognitive function in people who have had a previous stroke. Since most people with a recent stroke are taking a statin, trials might compare the intensity of statin treatment in preventing cognitive decline and dementia.

Q.9 Glossary

Acute coronary syndrome (ACS)	Acute coronary syndrome refers to a specturm of acute myocardial ischaemic states from unstable angina to transmural myocardial infarction
Absolute risk reduction	Absolute risk reduction refers to the difference in new events between the treatment under investigation and the placebo or comparator drug. If treatment A results in 5/1000 CVD events per year and treatment B results in 10/1000 CVD events per year, the absolute risk reduction is 10/1000 minus 5/1000 =5/1000 per year.
Atherosclerosis	A general term describing hardening, narrowing and loss of elasticity of arteries. It results from a deposition of rigid collagen in the arterial wall and also from the development of fatty plaques or atheroma on the inside of the artery wall. This increases the stiffness, decreases the elasticity of the artery wall and narrows the artery. The deposition of dietary fat as atheroma is the major factor in atherosclerosis which may be made worse by high blood pressure, smoking or other factors particularly when several factors are present at the same time. Atheromatous plaques may then be the site of blood clots that further narrow or even close the artery with resulting loss of oxygen and damage to the affected organ.
Cardiovascular event	Fatal or non-fatal myocardial infarct; acute coronary syndrome; fatal or non-fatal stroke; transient ischaemic attack
Cardiovascular risk (CVD)	The risk of a cardiovascular event occurring
Cardiovascular risk assessment	Involves the use of predictive equations and the adjustment of cardiovascular risk estimates based on clinical assessment or social factors such as ethnicity, family history or social deprivation or other relevant factors.
Cardiovascular outcomes	One or more of the following: death from stroke or myocardial infarction; non-fatal myocardial infarction or stroke; transient ischaemic episodes; acute coronary syndrome; angina; clinical interventions such as revascularisation are also considered as outcomes in some studies.
CVD: cardiovascula	In this document CVD refers to the combined outcome fatal and non-fatal myocardial infarction, fatal and non fatal stroke, transient ischaemic attack, angina

r disease	and acute coronary syndrome.
Clinical care pathway	A series of clinical processes that a patient might experience. For example CVD risk assessment – consideration of management options – treatment – follow-up.
Clinical risk stratification	A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy after the proposed interventions has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Evidence-based questions (EBQs)	Questions that are based on a conscientious, explicit and judicious use of current best evidence
High intensity statin	High intensity statin is the term used in the guideline to indicate statins whose effect on cholesterol lowering is greater than that of simvastatin 40mg. This includes simvastatin 80mg. The statin lowering effect of drugs at different doses are listed in table 7 in chapter 7.
Life-year	A measure of health outcome that shows the number of years of remaining life expectancy.
Median	The value at the halfway mark when data are ranked in order.
Myocardial infarction (MI)	Event that results in necrosis of heart muscle.
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome
Number needed to harm (NNH)	The number of people who need to be treated with a drug in order to harm one person in a set period of time.
Open-labelled randomised trial	A study in which patients are randomised to one treatment or another, and in which the clinician or investigator is aware of which treatment arm the patient is in.
Primary prevention	In the context of this document, primary prevention refers to interventions to modify lifestyle or drug treatments, in people who have not already got established cardiovascular disease. This particular guidance excludes people with diabetes.
Probabilistic sensitivity analysis	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Relative risk reduction	The relative risk reduction is the proportionate reduction in risk between the drug under investigation and a placebo or comparator drug. If treatment A results in 5/1000 CVD events per year and treatment B results in 10/1000 CVD events per year, the relative risk reduction is 5/10 =50%.
Secondary prevention	In the context of this document secondary prevention refers to interventions to modify lifestyle or drug treatments in people who already have established cardiovascular disease.

Q.10 Methods

Q.11 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the NICE in 'Clinical guideline development methods' (2006) (available at: http://www.nice.org.uk/).

Q.12 Developing key clinical questions

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs), specifying the interventions and outcomes to be searched for by the methodology team. These EBQs formed the basis for literature searching, appraisal and synthesis.

The total list of KCQs identified is shown in Appendix F. The methodology team and the GDG agreed that a full literature search and critical appraisal should not be undertaken for all of these KCQs in view of the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where literature searches and critical appraisal were essential. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in section 2.10 (The relationship between the guideline and other national guidance).

Q.13 Literature search strategy

The purpose of searching the literature is to identify published evidence that can be used to answer the clinical questions identified by the methodology team and the GDG. The Information Scientist developed search strategies for each searchable question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and relevant free text terms. Searches were conducted between September 2005 and August 2006. The Information Specialist agreed in advance with the Reviewer and Health Economist the sources to be searched for a given question. The parameters of literature searches, including any population limits and exclusions, were detailed on pro formas developed for each question. Updated searches for each question, to identify recent evidence, were carried out in April 2007. Full details of the sources and databases searched and the search strategies are contained in Appendix F.

An initial search for published guidelines or systematic reviews was carried out on the following databases or websites: National Electronic Library for Health (NeLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA).

If a recent, high quality, systematic review or guideline was identified to answer a clinical question, then in some instances no further searching was carried out.

Depending on the question, some or all of the following bibliographic databases were also searched to the latest date available: MEDLINE, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), PsycINFO, Allied & Complementary Medicine (AMED).

Q.14 Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if – based on abstract and title – they appeared relevant to the topic addressed in the GDG's question. The highest level of evidence was sought first. Wherever appropriate, the searches for evidence for both primary and secondary cardiovascular disease prevention were conducted simultaneously, and the results of these were then scanned to address separate questions. Where randomised controlled trials were not available, observational studies, surveys and expert formal consensus results were used. Only papers published in English were reviewed. Following a critical review of the full version of the study, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the GDG's clinical question and when it was either better or equivalent in quality to the research identified in the literature searches. Specialist advice was obtained from a dietitian, Alison Mead, to aid in the identification of useful terms for inclusion in searches for questions relating to lifestyle interventions.

The reasons for rejecting any paper ordered were recorded.

Q.15 Critical appraisal of the evidence

The Systematic Reviewer synthesised the evidence from the papers retrieved for each question or questions into a narrative summary. These formed the basis of this guideline. Each study was critically appraised using NICE criteria for quality assessment. The information extracted from the included studies is given in Appendices D and E. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

Q.16 Economic analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus, the starting point of an economic appraisal is to ensure that health services are clinically effective and cost-effective. Although NICE does not have a threshold for cost-effectiveness, interventions with a cost per quality adjusted life-year of up to £20 000 are deemed cost-effective, those between £20 000 and £30 000 may be cost-effective and those above £30 000 are unlikely to be judged cost-effective. If a particular treatment strategy was found to yield little health gain relative to the resources used, then it could be advantageous to redeploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of the different policy questions for this guideline, a comprehensive systematic review of the economic literature relating to primary and secondary prevention of cardiovascular disease was conducted. For selected components of the guideline original cost-effectiveness analyses were performed.

Literature review for health economics

The following information sources were searched: Medline (Ovid) (1966- April 2007), Embase (1980-April 2007), NHS Economic Evaluations Database (NHS EED), PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. The Information Scientist carried out the searches for health economics evidence. Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients at risk of or those who have had a cardiovascular event. Thus, patients who have had stroke, angina, peripheral artery disease, transient ischaemic stroke or myocardial infarction were considered for the secondary prevention section. Only papers written in English were considered.

The full papers were critically appraised by the health economist using a standard validated checklist (Drummond, M. F. and Jefferson, T. O., 1996). A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review.

Cost-effectiveness modelling

Some areas were selected for further economic analysis if there was likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use. For this guideline three areas were chosen for further economic analysis:

Cost-effectiveness of strategies for identification of patients at high risk of CVD in primary care

Cost-effectiveness of high intensity statins compared with lower intensity statins in patients with coronary heart disease

Cost-effectiveness of a strategy of 'titration threshold' (treating to target of 5mmol/l and 4mmol/l) compared with a strategy of using a standard dose of statin in people with CVD including a full incremental analysis.

Full reports for each topic are in Appendix C of the guideline. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were constructed in accordance with the NICE reference case outlined in the 'Guideline technical manual' (2007).

Q.17 Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with them.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

The recommendations and evidence statements were posted on an electronic forum. The discussion was reviewed at the next meeting and the recommendations finalised.

Q.18 Areas without evidence and consensus methodology

The table of clinical questions in Appendix F indicates which questions were searched.

In cases where evidence was sparse, or where the question was not deemed searchable, the GDG derived the recommendations via informal consensus methods, for example in the case of Question 23: 'How necessary is it to monitor liver function tests?'

In a few cases where there was a lack of consensus a formal vote was taken. Cooptees and GDG members with a declared interest did not vote.

Q.19 Consultation

The guideline has been developed in accordance with the NICE guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the drafts of the full and short versions of the guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by NICE.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the project team recorded the agreed responses.

Q.20 The relationship between the guideline and other national guidance

Q.20.1 Related NICE guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to the following guidelines when appropriate.

Published

Clinical guidelines:

MI: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org/CG048

Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from www.nice.org/CG043

Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org/CG033

Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/CG066

Public health intervention guidelines:

Brief interventions and referral for smoking cessation in primary care and other settings. NICE Public health intervention guidance 1 (2006). Available from www.nice.org/PHI001

Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NICE public health intervention guidance 2 (2006). Available from www.nice.org.uk/PHI002

Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008). Available from www.nice.org.uk/PH010

Technology appraisal guidance:

Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from www.nice.org.uk/TA132

Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org/TA094

Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. NICE technology appraisal guidance 39 (2002). Available from www.nice.org/TA039

Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/TA123

Under development

Familial hypercholesterolemia: identification and management. NICE clinical guideline. Publication expected August 2008.

Amended March 2010 Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

Q.20.2 Other national guidance

In formulating recommendations consideration was given to:

National Service Framework (NSF) for Coronary Heart Disease (2000).

JBS 2: Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice (2005)

Reference was made to the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/) for advice on cardioprotective dietary changes.

Reference was made to the Chief Medical Officer's report 2004 a: www.dh.gov.uk for advice on physical activity.

Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.

Q.21 Identification and assessment of people at high risk of cardiovascular disease (CVD)

Q.22 Recommendations

Full formal risk assessment

NICE Guidance Executive agreed in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for the assessment of CVD risk but should be considered one of the possible equations to use. The recommendations that relate specifically to the use and modification of the Framingham risk equation are indicated and listed in a separate section below.

1. **Healthcare professionals should always be aware that all CVD risk estimation tools can provide only an approximation of CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement.**

2. **Risk equations should be used to assess CVD risk.**

3. **This recommendation relates specifically to the use or modification of the Framingham risk equation – see below**

4. **Risk equations should not be used for people with pre-existing:**
   - **CHD or angina**
   - **stroke or transient ischaemic attack**
   - **peripheral vascular disease.**

5. **Risk equations should not be used for people who are already considered at high risk of CVD because of:**
   - **familial hypercholesterolaemia or other monogenic disorders of lipid metabolism**
   - **diabetes, see 'Type 2 diabetes: the management of type 2 diabetes (update)' (NICE clinical guideline 66). 8**

6. **This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.**

7. **When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold of 20% , healthcare professionals should consider other factors that:**
   - **may predispose the person to premature CVD, and**
   - **may not be included in calculated risk scores.**

8. **Ethnicity, body mass index and family history of premature heart disease should be routinely recorded in medical records.**

9. **This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.**

10. **This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.**

11. **This recommendation relates specifically to the use or modification of the Framingham risk equation – see below.**

12. **Socioeconomic status should be considered when using CVD risk scores to inform treatment decisions.**

13. Severe obesity (body mass index greater than 40 kg/m2) affects CVD risk and should be considered when using risk scores to inform treatment decisions (see 'Obesity', NICE clinical guideline 43).

14. CVD risk may be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Clinical judgement should be used to decide on further treatment of risk factors in people who are below the 20% CVD risk threshold.

15. CVD risk scores may not be appropriate as a way of assessing risk in people who are at increased CVD risk because of underlying medical conditions or treatments. These include people treated for HIV or with antipsychotic medication, people with chronic kidney disease and people with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.

16. People aged 75 or older should be considered at increased risk of CVD, particularly people who smoke or have raised blood pressure. They are likely to benefit from statin treatment. Assessment and treatment should be guided by the benefits and risks of treatment, informed preference and comorbidities that may make treatment inappropriate.

17. Recommendations relating specifically to the use and modification of the Framingham risk equation for the assessment of CVD risk. These recommendations should be considered when using Framingham risk equation.

18. The following variables should be used for formal estimation of CVD risk with the Framingham 1991 equations:

- **age**
- **sex**
- **systolic blood pressure (mean of previous two systolic readings)**
- **total cholesterol**
- **HDL cholesterol**
- **smoking status**
- **presence of left ventricular hypertrophy.**

19. Healthcare professionals should be aware that Framingham 1991 risk equations may overestimate risk in UK populations.

20. The estimated CVD risk should be increased by a factor of 1.5 in people with a first-degree relative with a history of premature CHD (age at onset younger than 55 in fathers, sons or brothers or younger than 65 in mothers, daughters or sisters).

21. The estimated CVD risk should be increased by a factor of between 1.5 and 2.0 if more than one first-degree relative has a history of premature CHD.

22. The estimated CVD risk for men with a South Asian background should be increased by a factor of 1.4.

Lipid measurement

23. Both total and HDL cholesterol should be measured to achieve the best estimate of CVD risk equations.

24.3 Before starting lipid modification therapy for primary prevention, people should have at least one fasting lipid sample taken to measure total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

25. People in whom familial hypercholesterolaemia or other monogenic disorders are suspected because of a combination of clinical findings, lipid profiles and family history of premature CHD should be considered for further investigation and specialist review.

26. People with severe hyperlipidaemia should be considered for further investigation and/or specialist review.

Q.23 Assessment of cardiovascular risk

Q.23.1 Introduction

Estimates of CVD risk derived from equations are not an exact science but are better than clinical judgment alone for the estimation of CVD risk.

A number of risk assessment equations are available that estimate cardiovascular risk in individuals. They have been derived from studies of individuals who have been followed up often for substantial lengths of time. Risk assessment equations predict risk best in the type of population from which they were derived. Equations derived from North American populations from the 1960s to the 1980s when coronary heart disease (CHD) was at its peak overestimate risk in contemporary European populations by around 100% in Southern European populations and by 50% or more in Northern European populations including the UK. Conversely, such equations may underestimate risk in populations such as people with diabetes, South Asian men or the most socially deprived who are at higher than average risk.

Q.23.2 Evidence statements for assessment of cardiovascular risk

Different risk assessment methods exist. The most widely used and researched are derived from the Framingham cohort.
In representative populations, recognised Framingham-based methods offer reasonable discrimination between high- and low-risk individuals but tend to overestimate the absolute risk of CVD in lower risk populations and underestimate risk in high-risk populations. There has been concern that estimates derived from North American populations dating back 30 years may not accurately estimate risk in contemporary European populations when CHD mortality has fallen by more than half during this period. Overall the Framingham risk equation is likely to overestimate risk in the current UK population, more so in Southern England than Northern England or Scotland.
Framingham-based methods may underestimate risk in people at high risk such as people with a strong family history of premature CVD, certain ethnic groups and those from relatively socio-economically deprived backgrounds. They may also underestimate risk in people with extreme risk factors or other clinical risks not included in the model.
There are no consistent differences in the generalisability of one Framingham model over another.

The following endpoints have been used by the statin technology appraisal report to establish treatment thresholds: fatal and non-fatal myocardial infarction, acute coronary syndrome, stable angina, stroke, and transient ischaemic attacks. (NICE technology appraisal 94, 'Statins for the prevention of cardiovascular events').
When used in conjunction with the Framingham estimates, those defined by the NICE Technology Appraisal are the most appropriate. When considering management strategies based on other risk equations, endpoints such as revascularisation, peripheral arterial disease and other disease processes associated with atherosclerosis may also be relevant.
Framingham based risk scoring methods do not accurately estimate risks in some groups of people.
Several risk factors have not been included in the Framingham risk equations and some adjustment of this risk estimate may be required to more accurately represent an individual's absolute risk: • Family history of a premature event from CVD: first-degree male relatives under the age of 55 years and first-degree female relatives under the age of 65 years • Ethnic group • Socio-economic status • People already on treatment that modifies CV risk • Extremes of risk factors, for example people who have a body mass index over 40 kg/m2.
There are differences in cardiovascular risk between black and minority ethnic groups and the white population in England and Wales.
For men, the risk of CVD was higher in South Asian ethnic groups (with some subgroup heterogeneity) than for men in the white population.
For men there is no robust evidence for a difference in the risks of CVD other than that between men from South Asian ethnic groups and the general population.
For women there is no robust evidence for a difference in the risks of CVD between South Asian ethnic groups (with considerable subgroup heterogeneity) and the general population.
There is increased risk of CVD in people with a family history of premature CVD.
Cohort studies have shown a consistent association between having a positive family history of CVD and an increased risk of developing CVD. This risk remains even when adjusted for age, socioeconomic status, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking status. The exact relative risk varies according to sex and nature of relationship between the individual with premature CVD and the index case.
The younger the age at which the family event occurred and the greater the number of family members involved, the greater the relative risk.
Cardiovascular risk is closely associated with socio-economic status. Framingham equations do not include socio-economic status and underestimate risk in people who are relatively socially deprived. The use of equations that do not include a measure of socio-economic status may exacerbate inequalities in CVD.
ASSIGN is a CV risk score developed in a Scottish cohort that includes similar variables to Framingham in addition to an index of social status based on postcode of residence at recruitment, and family history of CVD.
The ASSIGN score improved discrimination of estimated 10 year CVD risk in a Scottish cohort

compared with Framingham.
Observed CVD risk in the Scottish cohort varied significantly according to socioeconomic status. Framingham risk score estimates did not reflect this significant variation, while estimates using the ASSIGN score correlated with socioeconomic status
QRISK is a new risk score that has been developed using routine data from UK electronic primary care patient records.
QRISK includes social deprivation, family history, body mass index and antihypertensive treatment that are not included in the Framingham equation.
Initial validation of the QRISK score in a UK electronic primary care patient cohort found that QRISK was a better discriminator of CVD risk compared with the Framingham risk score.
The performance of the QRISK score for predicting CVD risk was assessed in a second UK medical records database. A revised equation for QRISK was used that improved the method for multiple imputation of missing data by including the following; binary variables for diagnosis of hypertension and incident diabetes, and continuous variables for the number of prescriptions for aspirin, statins and antihypertensive treatments for each patient during the study period. A correction was also made regarding the total cholesterol to HDL cholesterol ratio. The revised QRISK score was more predictive of CVD risk in the second UK cohort compared with the Framingham risk score.
Little evidence was found supporting or refuting the assumption that CVD assessment by clinicians improves health outcomes. The interventions showed no improvement in predicted absolute CVD risk or in declared primary outcomes.
A study in hypertensive patients has shown a small reduction in systolic blood pressure associated with the use of a risk chart but not when used in conjunction with a computer based clinical decision support system.
Another study has shown very low uptake of risk-scoring methods by clinicians that would have obscured any beneficial effect on blood pressure by the intervention.
The accuracy of use of chart based systems has been questioned. Current evidence is an insufficient basis on which to judge the effectiveness of CVD risk estimation as a method of improving health outcomes.

Q.23.3 Methods for multiple risk factor assessment to estimate absolute cardiovascular risk in people who are at risk of CVD

A recent systematic review[175] (Appendix J) was used as the evidence source. Literature searching beyond the search date of the systematic review identified two further risk scores developed in UK populations (QRISK discussed in section 3.3.5, and ASSIGN discussed in section 3.3.5). The Beswick et al systematic review compared the accuracy of risk scoring methods such as charts and tables compared with full prediction models, namely, the Framingham-Anderson model of 1991.[90] A complete reference to the materials and evidence reviewed is given in Appendix J.

Eleven derived risk charts, tables and nomograms were identified comparing risk calculations with the original Framingham-Anderson prediction model (1991).

The tools identified were as follows:

- Sheffield tables (2 versions)[616,1131,1398]

- Joint British Societies (JBS) charts (2 versions)[15,20] European Societies (JBS) charts (2 versions).[345,1444]
- Canadian nomograms[941]
- New Zealand charts (3 versions)[13,705,947]
- World Health Organization and the International Society for Hypertension (WHO-ISH) chart http://www.ish-world.com/default.aspx?Guidelines.

It was found that the early versions of the Sheffield Tables[616,1131] and the Joint European Societies charts[345,1444] had poor sensitivity as they did not include individual values for HDL cholesterol in the risk calculation. More recent Sheffield tables[1398] and Joint British Society charts[15,20] show reasonable sensitivity and specificity compared with the full Framingham Anderson model. The 1997 Canadian nomograms[941] included HDL cholesterol in their risk calculation however they were very poor at identifying patients at high levels of risk. The WHO-ISH 1999 table suffers from generalisation of the Framingham-Anderson model with risk factor counting substituting for continuous clinical variables. The New Zealand charts have only moderate sensitivity and specificity and provide assessment of CVD risk.[13,705,947] The most recent Joint British Society charts estimate CVD risk but were not available at the time of this review.

In conclusion, the systematic review by Beswick et al[175] (Appendix J of the full guideline) showed that comprehensive information is required in risk tables and charts. The inclusion of HDL cholesterol gives the most accurate estimate of cardiovascular risk.

Q.23.4 Endpoints used for assessment when estimating cardiovascular risk

The choice of CVD endpoint is important as it affects the numbers of people reaching treatment thresholds and the numbers targeted for risk reduction treatments.

The endpoints recommended in this guideline are the same as those used in the NICE Technology Appraisal 94: Statins for the prevention of cardiovascular events (2006). The scope for this guideline includes risk factor modification for symptomatic atherosclerotic vascular disease including revascularisation and peripheral arterial disease and these endpoints should be included where appropriate in other recommended risk equations.

Q.23.5 Adjustments to Framingham cardiovascular risk estimates

Adjusting the calculated Framingham cardiovascular risk estimate by other risk factors

A systematic review by Brindle et al[218] (Appendix J) reviewed the accuracy of Framingham-based methods to estimate risk in populations other than those in which the models were derived (external validation).

Data were extracted on the ratio of the predicted to the observed 10-year risk of CVD and CHD from 27 studies with data from 71,727 participants. These studies used either the Framingham-Anderson (1991)[90] or Wilson[1436] risk scores (methods using the outcomes of combined fatal and non-fatal CHD or CVD) and covered a wide range of different population groups: Populations varied in nationality, age range and sex, date of recruitment and outcomes studied. The groups studied were representative samples of men and women, people with diabetes, people with raised cholesterol, people on treatment for hypertension, people with no CHD determined by angiography and people with a family history of CVD.

For CHD, the predicted to observed ratios ranged from 0.43 in a study of people with a family history of CHD (that is, predicting a lower risk than was observed) to 2.87 in a study of women from Germany (PROCAM) (that is, predicting a much higher risk than was observed).[638] Under-prediction was observed in studies of higher risk patients such as those with diabetes, a strong family history of

premature CVD, people from geographical areas with a high incidence of disease and people in socio-economically deprived groups.

For CVD, there was similar trend of increasing under-prediction with increasing risk of the population.

Over-prediction of risk occurs when Framingham equations are applied to populations with a lower baseline risk than that experienced by the Framingham cohort. Over-prediction was seen in lower and medium risk primary care and occupational populations in Germany[638], France and Northern Ireland[465] and a US screening cohort with a medium level of observed risk.[581] In the multicentre clinical trial of Bastuji-Garin et al, CHD risk was over-estimated and this was seen across eight Western European countries and Israel.[148] Within England, Wales and Scotland, over-prediction by the Framingham equations occurred in all regions but was greater in the South and the Midlands/Wales where there was relatively lower mortality and morbidity than in Scotland and the North of England.[220]

This systematic review shows that the accuracy of the Framingham risk estimates cannot be assumed, and that it relates to the background risk of CVD in the population to which it is being applied. Over-estimation of risk tends to occur in populations with low observed risk and underestimation in high-risk groups.

Adjustment of the Framingham cardiovascular risk score to take account of ethnicity

The rates of CVD vary between ethnic groups; however, the Framingham risk score does not take ethnicity into account as a risk factor.

Studies were identified which provide evidence for differences in risk by ethnic group in the UK and the need to adjust risk estimates to take into account ethnic origin when estimating an individual's risk of CVD.[268,1120]

The method of adjustment was considered in three papers. Bhopal et al's[179] paper included 6448 men and women aged 25 to 74 years from the Newcastle Health and Lifestyle Survey. The hazard ratio adjusted for age and sex for CHD death in South Asians combined compared with Europeans was 2.23 (95% CI 1.13 to 4.38), the corresponding ratio for stroke mortality was 1.35 (95% CI 0.32 to 5.7).

A study by Aarabi and Jackson[49] used risk factor data from 4497 individuals identified from the Health Surveys for England 1998 and 1999, who were eligible to have their risk of a first CHD event calculated by the Framingham equation. Arabi and Jackson considered adding 10 years to the age of South Asian people as the simplest way of calculating CHD risk using paper based methods. The validity of this method, which assumes an excess risk of 1.79, is uncertain.

The study by Brindle et al[219] included 3,778 men and 4544 women aged 35 to 54 years from the Health Surveys for England 1998 and 1999 and the Wandsworth Heart and Stroke Study, both of which are community-based surveys. The authors estimated the incidence rate from prevalence data for 7 minority ethnic groups: Indians, Pakistanis, Bangladeshis, black Caribbean, Chinese (from the Health Surveys for England 1998/99) and black Africans (from the Wandsworth Heart and Stroke Study). The incidence rate was estimated because of the lack of prospective data on British black and minority ethnic groups.

The sex-specific and age-standardised prevalence ratio for CHD and for CVD for each ethnic group compared with the general British population was obtained from the Health Surveys for England 1998/99. Separate risk estimates were developed for CHD and CVD for both men and women for each ethnic group.

Calculated age-adjusted CVD prevalence ratios for seven ethnic groups showed considerable variation. In men, the highest ratio was observed in Bangladeshis (HR1.39, CI 0.82 to1.96) and the lowest among Chinese (HR0.49, CI 0.16 to 0.82); in women, the highest ratio (HR1.33, CI 0.70 to 1.96) was in Pakistanis and the lowest (HR 0.22, CI 0 to 0.53) among Chinese.

This model has not been validated.

In summary, there is consistent evidence to support the need for adjustment of Framingham risk estimates to take account of ethnicity in UK populations but the best method for achieving this remains uncertain. Current guidance by the Joint British Societies[237],[1445] recommends multiplying the Framingham score by a correction factor of 1.4 for South Asian people; however, this does not acknowledge the difference between the sexes. There are particular problems in estimating risk for people of Afro-Caribbean origin who have a higher risk of stroke but a lower risk of ischemic heart disease.

It was noted that the determination of ethnicity itself is problematic despite much debate.[551] It is a multidimensional concept and embodies one or more of the following: 'shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and lead to a sense of identity and group; and a common language or religious tradition'. For pragmatic reasons the self-determined Census question on ethnic group is acceptable. South Asian is a broad category and is generally defined as people assigning themselves as Indian, Pakistani, Bangladeshi and Sri Lankans.

The GDG agreed with the data compiled by Brindle et al[219] that indicated that a risk estimate 1.4 times that of the white population was the most appropriate weighting to use for adjustment of the Framingham equation in men of South Asian origin. There was no significant increase in risk among South Asian women. Although some other ethnic groups had low levels of risk in comparison to white people, this was not sufficiently robust on which to base a recommendation.

Adjustment of the Framingham cardiovascular risk score to take into account family history

Three studies were found addressing the extent to which family history predicts risk. These studies are the Framingham Offspring Study by Lloyd-Jones et al[857] the Malmo Preventive Project (MPP) by Nilsson et al[1029] (follow up study) and the Physicians' Health Study (PHS) and the Women's Health Study (WHS).[1231]

The Framingham Offspring Study

Lloyd-Jones et al[857] determined whether parental CVD predicts offspring events independent of traditional risk factors. The population consisted of 2302 men and women with a mean age of 44 years in the Framingham Offspring Study, who were free of CVD and whose parents were both in the original Framingham cohort. The authors examined the association of parental CVD with an 8-year risk of offspring CVD using pooled logistic regression.

Compared with the participants with no parental CVD, those with at least 1 parent with premature CVD (onset age < 55 years in father, < 65 years in mother) had a greater risk for events, with age-adjusted odds ratios of 2.6 (95% CI 1.7 to 4.1) for men and 2.3 (95% CI 1.3 to 4.3) for women. Multivariate adjustment resulted in odds ratios of 2.0 (95% CI 1.2 to 3.1) for men and 1.7 (95% CI 0.9 to 3.1) for women. Non-premature parental CVD and parental coronary disease were weaker predictors.

The Malmo Preventive Project (MPP)

Nilsson et al [1029] studied the adjusted relative risk of CVD events in offspring of parents with cardiovascular mortality before 75 years. A total of 22 444 men and 10 902 women attended a

screening programme between 1974 and 1992 and were followed up through national record linkage.

There was an increased risk of CVD events (mortality and morbidity) in offspring in relation to a positive family history of parental CVD mortality before 75 years. The multivariate adjusted relative risk (RR) for father-son heritage was 1.22 (95% CI 1.02 to 1.47; P < 0.05), for mother-son heritage, RR = 1.51 (95% CI 1.23 to 1.84, P < 0.001), for father-daughter heritage, RR = 1.20 (95% CI 0.83 to 1.73) and for mother-daughter heritage, RR = 0.87 (95% CI 0.54 to 1.41).

Subdividing parental age of early death into age groups 50-68, 69-72 and 73-75 years showed a graded association for maternal influence: RR = 1.82 (95% CI 1.35 to 1.46), 1.55 (95% CI 1.14 to 2.10) and 1.50 (95% CI 1.13 to 1.98) respectively but not for paternal influence, RR 1.29 (95% CI 0.99 to 1.69), 1.08 (95% CI 0.81 to 1.44) and 1.40 (95% CI 1.12 to 1.76) respectively using surviving parents or mortality after 75 years as the reference group.

The Physicians' Health Study (PHS) and the Women's Health Study (WHS)

Sesso et al[1231] prospectively studied 22 071 men from the Physicians' Health Study (PHS) and 39 876 women from the Women's Health Study (WHS) with data on parental history and age at MI.

Compared with men with no parental history, those with a maternal, paternal and both maternal and paternal history of MI had a RR of CVD of 1.71, 1.40 and 1.85 respectively; among women, the corresponding RRs were 1.46, 1.15 and 2.05 respectively.

Sesso et al[1231] also looked at the effect of parental age: For men, maternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79 and ≥ 80 years had RRs of 1.00, 1.88, 1.88, 1.67 and 1.17. For women, the RRs for maternal age at MI of < 50, 50 to 59 and ≥ 60 years were 2.57, 1.33 and 1.52. Paternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79 and ≥ 80 years in men had RRs of 2.19, 1.64, 1.42 1.16 and 0.92; in women, for paternal age at MI of < 50, 50 to 59 and ≥ 60 years, the RRs were 1.63, 1.33 and 1.13.

The GDG noted that there was a continuous distribution of risk, which tended to increase the younger the age at which the family member had an event. Increased risk was noted to be present even up to age 75 years. The number of family members was also related to risk, and risk was greater where female relatives were affected. For simplicity the GDG considered that risk should be adjusted by 1.5 where there was a history of female first-degree relative under 65 years with CHD or a history of first-degree male relative under 55 years. Additional family members in this category would further increase risk. If more than one first-degree relative is affected, the risk estimate should be increased by a factor of up to 2.0.

Adjustment of the Framingham cardiovascular risk score to take into account socio-economic status

There is a widening relative gap in mortality and morbidity associated with socio-economic status. There has been a substantial reduction in CVD in the past two decades but the poorer sections of society have not improved as fast as the more affluent. In 1986 to 1992 mortality from circulatory disease was 69% greater in people from social classes IV and V than that in people in social classes I and II and by 1997 to 1999 this had increased to 86%[1426]. This represents a decrease between socio-economic groups in absolute mortality difference but a widening of the relative difference. This relative inequality has been a cause for governmental concern and tackling health inequalities in CVD is a major component of current governmental strategy[420]. Mortality from circulatory diseases in the most deprived category is currently threefold higher in women and 2.7 times higher in men than in the least deprived category.

General cardiovascular risk score developed for use in primary care

At the end of the development of this guideline a study was published on the use of a new cardiovascular risk score for use in primary care. This study was not reviewed by the GDG because its publication occurred after formal discussion of the evidence for cardiovascular risk assessment. The study identified participants from the original Framingham Heart study and the Framingham Offspring study. A sex specific multivariable risk factor algorithm was developed that included the following; age, total and HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status. This general algorithm was used to evaluate the risk of developing a first CVD, and it showed good calibration and discrimination for combined CVD events over 12 years of follow-up. It also showed good calibration for the following individual outcomes; coronary artery disease, stroke, peripheral artery disease or heart disease. A simpler CVD risk equation that was developed for use using non-laboratory predictors (body mass index substituted for total and HDL cholesterol) showed reasonable discrimination for the estimation of risk compared with the general CVD algorithm.[372]

Q.23.6 ASSIGN

During the course of the development of this guideline, the Scottish ASSIGN score has been published and adopted as part of SIGN guidance. ASSIGN was developed from the Scottish Heart Health Extended Cohort (SHEC), which was a series of population studies from the 1980s to 1990s which were followed up until the end of 2005.[1448] Participants qualified for inclusion in the analysis if they met the following criteria; risk factor data available, permitted follow up, aged 30 to 74 years at recruitment, reported neither coronary artery disease or stroke, no preceding hospital diagnosis of coronary heart disease, stoke or transient ischaemic stroke. The endpoints for the ASSIGN score were; deaths from cardiovascular disease or any hospital discharge of diagnosis of coronary heart disease or cerebrovascular disease post recruitment, or first coronary intervention.

There were 6540 men and 6757 women in the study and the mean age at recruitment was 48.8 years. Follow up at 30th December 2005 ranged from 10 to 21 years. Of 6540 men, 4936 remained disease free and 1604 developed disease, 743 within 10 years. Of 6757 women, 5742 remained disease free and 1015 developed cardiovascular disease, 422 within 10 years. The ASSIGN score incorporated similar risk factors to Framingham which were entered as continuous variables rather than categories, in addition to, an index of social status based on postcode of residence at recruitment (Scottish Index of Multiple Deprivation, SMID) and family history of cardiovascular disease. The ASSIGN score was compared with Framingham score (working model comparing the scores at www.assign.com). The rank correlations between Framingham and ASSIGN were 0.92 for men and 0.90 for women. ASSIGN scores while lower on average, correlated closely with Framingham, and the discrimination of risk in the SHHEC was significantly, but marginally improved by ASSIGN. The predicted 10 year cardiovascular risk overall for men using ASSIGN was 14.4% and using Framingham was 16.0%. The observed incidence was 11.7%. The distribution of the risk scoring was highly skewed. The median ASSIGN value in the SHHEC population was the same as the observed incidence at 11.6%, while for Framingham it was 13.6%. The predicted 10 year cardiovascular risk overall for women using ASSIGN was 9.3% and using Framingham was 9.6%. The observed incidence was 6.4%. The median ASSIGN value in the SHHEC population was the similar to the observed incidence (6.2% versus 6.4%) while for Framingham it higher at 7.1%. A previous report by the authors found that the SIMID correlates highly with coronary risk when compared across population fifths in the SHHEC population.[1356] Observed risk had a steep gradient according to social status, varying two fold in men at the top (least) and the bottom (most deprived) fifth of the population (from 4.9% to 10.0%), and fivefold, although at lower levels in women (from 1.1% to 5.5%). Hence the relative risk of observed 10-year CVD risk (sexes combined) analysed across population fifths from least to most deprived was 1.00, 1.81, 1.98, 2.22, and 2.57. Expected risk based on Framingham had one quarter of the gradient, and gave relative risks of 1.00, 1.17, 1.19, 1.28, and 1.36).[1356] Comparison of the performance of ASSIGN versus Framingham by fifths of the SIMD score found that ASSIGN abolished this gradient, while it remained significant for the expected risk from the

Framingham score versus the observed event rate. Hence ASSIGN classifies more people with social deprivation and anticipates more of their events compared with Framingham. [1448]

Q.23.7 QRISK

During the last phase of the development of the guideline a new CVD risk score, QRISK, has been derived and validated using data from a UK primary care population.[651] Data were retrieved from the QRESEARCH database (www.qresearch.org), a large electronic database representative of primary care, and containing the health records of 10 million patients over a 17 year period from 529 general practices using the EMIS computer system. QRESEARCH contains area measures of ethnicity and also deprivation (Townsend score) based on the 2001 UK census, and linked to every patient's record. Information from two thirds of the QRESEARCH database was used for modelling dataset and the remaining third was used for validation dataset. An open cohort of patients aged 35 to 74 years at the date of study entry was identified that was drawn from patients registered from 1 January 1995 to 1 April 2007. The following patient groups were excluded; those with diabetes or CVD before their entry date into the database, temporary residents or those with interrupted periods of registration at the practices and 4% of patients that did not have a valid postcode ethnicity score.[651]

The primary outcome was the first recorded diagnosis of CVD (including MI, CHD, stroke and transient ischaemic attack) on the general practitioners clinical computer system, either before or at death occurring between 1 January 1995 and 1 April 2007. The following risk factors were included in the analysis using the closest to the entry date to the cohort for each patient and imputing missing values when necessary; age (in single years), sex, smoking status (current smoker, non smoker-including former smoker), systolic blood pressure (continuous), ratio of total serum cholesterol to high density lipoprotein levels (continuous), left ventricular hypertrophy recorded on clinical records (yes or no), body mass index (continuous), family history of CVD in first degree relative aged less than 60 years (yes or no), body mass index (continuous), Townsend deprivation score, percentage of South Asian residents at output areas, current prescription of at least one antihypertensive (yes or no). A Cox proportional hazard model was used to estimate the coefficients associated with each potential risk factor for the first ever recorded diagnosis of CVD for men and women separately. The variables to be included in the model were specified a priori. Models were compared using the Bayes information criterion (a likelihood measure which in lower values indicate better fit, and in which a penalty is paid for increasing variables). The strength of the association between one unit increases in each continuous risk factor was examined, and categories for other variables such as smoking compared with non-smoking were compared. The proportional hazards model's assumptions were tested for any non-linear relation between continuous independent variables and the outcome. Interactions between systolic blood pressure and antihypertensive treatment and also between smoking and deprivation were examined. The log of the hazard ratios for each of the risk factors (the coefficients from the Cox regression) from the model were used as weights for the new CVD risk equation. An estimate of each patient's probability of experiencing a CV event was made by combining these weights, the characteristics of the patient, and also using the baseline survivor function for all participants. The baseline survivor function was estimated from the Cox regression model centred on the means of continuous risk factors, and the value for 10 year follow-up was extracted.[651]

The performance of the risk equation in the derivation dataset (QRISK score) was tested in the validation dataset by calculating the 10 year estimated CVD risk for each patient in the dataset. Missing values for continuous variables were replaced with mean values obtained from the derivation dataset by five-year age-sex bands, and assuming patients were non smokers if status was not recorded. Calibration (the degree of accuracy) was assessed by calculating the mean predicted risk of CVD at 10 years and the observed risk at 10 years obtained using the 10 year Kaplan-Meier estimate. The ratio of the predicted to the observed CVD risk for patients was then compared in patients in the validation cohort in each tenth of predicted risk. The predicted and observed risks

were also compared for men and women by age band and fifth of the Townsend score. Discrimination was assessed by receiver operated curve, and also by the R2 and D2 statistics (measures of discrimination and explained variation for survival models). The performance of QRISK was compared to the Framingham and ASSIGN equation.[651]

There were 478 UK practices that met the study inclusion criteria, 318 practices were randomly assigned to the derivation dataset (total patient number aged 35 to 74 years = 1 283 174, 50.4% women) and 160 practices to the validation dataset (total patient number aged 35 to 74 years = 614 553, 50.3% women). In the derivation dataset there were 65 671 incident cases of CVD and these were higher in men than women. The median follow up was 6.5 years and 306 259 patients were followed up for at least 10 years. The 10 year observed risk of a CV event in women was 6.69% (95%CI 6.61% to 6.78%), and in men was 9.46% (95%CI 9.36% to 9.56%). In the validation dataset, the 10 year observed risk of a CV event in women was 6.60% (95%CI 6.48% to 6.72%), and in men was 9.46% (95%CI 9.14% to 9.43%). The final Cox regression model used in the study included the logarithm of age, ratio of serum cholesterol to HDL cholesterol, systolic blood pressure, body mass index, family history of premature CHD, smoking status, Townsend deprivation score, and the use of at least one blood pressure treatment. The final model also included an interaction term between systolic pressure and blood pressure treatment. Left ventricular hypertrophy and the area measure of ethnicity were omitted. Hazard ratios for the final Cox regression analysis showed in the risk of CVD was increased with increasing age, body mass index and Townsend deprivation score. The risk was higher in patients who smoked, had a family history of CVD, and were receiving antihypertensive therapy. The hazard ratio for the ratio of total cholesterol to HDL cholesterol was just above and close to one, but it had been decided to include this factor a priori.[651]

From the calibration and discrimination modelling, the Framingham equation over-predicted risk at 10 years by 35%, ASSIGN by 36% and QRISK by 0.4%. All three equations tend to over predict risk in the lowest three tenths of risk at 10 years, the greatest over prediction occurred with ASSIGN, followed by Framingham and then QRISK. The receiver operator curve (ROC) statistic indicated that the final QRISK score had at least as good as, if not slightly better discrimination than the Framingham and ASSIGN equations. The R2 statistics (standard error) for QRISK, Framingham and ASSIGN for women were; 36.4% (0.43), 31.7% (0.44) and 34.1% (0.43), respectively. The D2 statistics (standard error) for QRISK, Framingham and ASIGN for men were; 33.3% (0.39), 29.1% (0.38) and 30.5% (0.38), respectively. Comparison of the proportion of patients with a CVD risk score ≥ 20% by Townsend fifths and sex for the three risk prediction scores found that the biggest difference was observed in women. QRISK predicted 9.8% of women aged 35 to 74 years from the most deprived fifth to be at high risk compared with 3.0% of women from the most affluent fifth. The corresponding values for the Framingham equation were 6.3% (most deprived) and 4.6% (most affluent). QRISK predicted 12.6% of men from the most deprived areas to be at high risk compared with 9.6% of those from the most affluent areas. The values for the Framingham equation were 19.5% (most deprived) and 20.5% (most affluent). Overall, QRISK predicted 8.5% of patients aged 35 to 74 years to be at high risk compared with 12.8% for the Framingham equation and 14.0% for ASSIGN. Using QRISK, 34.5% of women and 72.9% of men would be at high risk compared with 24.1% and 86.0% using the Framingham equation.[651]

The performance of the QRISK score for predicting CVD risk was assessed in a second medical records database; The Health Improvement Network (THIN). This new electronic database contains records from general practices, some of which have or continue to participate in the General Practice Research Database (GPRD) and others that have never participated in the in GPRD. Hippisley-Cox et al identified the second cohort of patients from the THIN database, with the same inclusion and exclusion criteria as that for the original study[651], registered between 1 January 1995 and 31 March 2006. A Framingham score and QRISK score was generated for each individual patient in the THIN cohort and also the validation QRISK cohort. Hippisley-Cox et al used a revised equation for QRISK that had taken account of improvements in the method for multiple imputation of missing data. In addition to the original variables, the following were included in the imputation model; binary

variables for diagnosis of hypertension and incident diabetes, and continuous variables for the number of prescriptions for aspirin, statins and antihypertensive treatments for each patient during the study period. The revised equation excluded patients taking statins at baseline. The revised QRISK equation also corrected for an analytical error in the first published QRISK equation, which had found that the total cholesterol to HDL cholesterol ratio was of borderline significance. Following this correction, the current published QRISK equation shows that the total cholesterol to HDL cholesterol ratio is highly predictive of CV risk. The adjusted hazard ratios for the ratio of cholesterol to HDL ratio was 1.20 (95% CI 1.17 to 1.22) in females and 1.25 (95% CI 1.23 to 1.27) in males (see QRISK authors' response http://www.bmj.com/cgi/eletters/335/7611/136#174181).[651]

There were 1 072 800 patients in the THIN cohort that were analysed (529 813 men (49.39%)). The corresponding cohort on QRESEARCH had 607 733 patients. The baseline characteristics were similar for THIN and QRESEARCH for age, sex, risk factors and medication, however, the family history of premature CHD was substantially lower in THIN than QRESEARCH (3.5% in males in THIN versus 9.2% in males in QRESEARCH). The Framingham equation over predicted risk by 28% in the THIN cohort while, QRISK under predicted by 10%. QRISK performed better than Framingham for the discrimination and calibration statistics (receiver operator curve statistic, R2 statistic, D2 statistic). The validation statistics for both QRISK and Framingham were similar in the THIN cohort and the QRESEARCH cohort.[651]

Q.23.8 Cost- effectiveness of assessment of cardiovascular risk

There is no cost effectiveness evidence regarding the choice of tool. Refer to Section 4.2.3 of the full guideline.

Q.23.9 Evidence to Recommendations

One of the most difficult decisions that the GDG faced during development was that of recommending a risk assessment equation. First, the evidence base in this area is rapidly developing with two new risk scores being published in the UK during the development of the guideline. Second, after reviewing the research evidence, in the view of the GDG, all available equations had significant limitations.

Conduct of meetings and discussion

In the initial development of the guideline the evidence presented to the GDG involved the choice of which Framingham risk equation to use and how that equation could be adapted. All members of the GDG took part in the discussions and decisions.

Towards the end of the development of the guideline two members of the GDG, one of whom was the chairman, declared an interest as researchers involved in the development of the new QRISK score and related publications. This was a conflict and they were treated as experts for these discussions. They were invited to present the case for QRISK but not to participate in the discussion unless asked a direct question. They left the room prior to voting and the GDG conducted their final deliberations in their absence and voted. Discussions related to risk scores was chaired by the NCC-PC lead /Clinical Director.

The other members of the GDG were asked to declare interests in other existing risk scores. Several declared previous or ongoing work in relation to risk scores (refer to the Declatation of Interests in Appendix L) such as supervising PhD students investigating the use of risk scores, research on validation and adaptation of risk scores, and co-authors of reports that recommended adaptations to Framingham for the UK population. All GDG members declared these interests and all members were aware of them during discussions, but they were not regarded as significant conflicts which required exclusion from the discussion or voting.

The expert co-opted onto the GDG for secondary prevention, took part in the discussions but did not vote.

Background

The Framingham equation, as detailed above, is based on a U.S. population and has been the dominant method of calculating risk, despite its limitations, and is familiar to clinicians.

Early in the development the GDG discussed the limitations of Framingham equation including:

- The tendency of Framingham equation to over estimate risk in contemporary European populations
- The tendency of Framingham equation to under-estimate risk in people from deprived backgrounds
- The difficulties in adjusting Framingham in clinical practice when patients may already be on BP treatment
- Difficulties in adjusting Framingham for additional known risk factors such as a family history of CHD,
- Framingham equation being based on a fixed population with baseline data collected in the late 1960s and 1970s.

The GDG recognized the potential value of a risk score developed in the UK population and in the later stages of development of the guideline the GDG became aware of the development of the QRISK equation and invited the principal investigator to attend a GDG meeting and present the preliminary findings.

Discussion

At the time of the first consultation of this guideline, there was no published research on QRISK equation and the GDG only had preliminary data available to them. Based on the published evidence, the GDG recommended the Framingham equation. They examined the existing literature on adjustments to Framingham and recommended how the Framingham equation should be adjusted to the UK population.

The GDG met again in September 2007 to consider stakeholder comments on the draft guideline. The first paper describing QRISK[651] and the rapid responses to that paper including authors reply (http://www.bmj.com/cgi/content/short/bmj.39261.471806.55v1) had been published. The GDG also had access at this time to a second unpublished paper validating QRISK and addressing many of the criticisms in the original paper. The second paper is now published. [652]

The performance of QRISK in this primary care population was better than the Framingham equation across each statistical measure. It reclassified a greater proportion of people from deprived backgrounds as being at high risk, relative to Framingham, as it took into account the increased risk associated with social deprivation. It appeared to address many of the limitations of Framingham because;

- in addition to standard risk factors QRISK includes variables relating to
  - Social deprivation (Townsend score)
  - Being on BP treatment
  - Having a family history of CHD
  - Body Mass Index
- QRISK can be regularly updated and so keep up with secular changes in CVD incidence
- QRISK uses current primary care data to derive a risk score in the population in which it is to be used. i.e. UK primary care.

At the time of this meeting (September 2007) the GDG had two main concerns about recommending QRISK:

1. The GDG did not have the technical skills to assess the appropriateness and accuracy of the advanced statistical techniques (i.e. multiple imputation) employed.

2. Only one paper[651] had been published and subject to scientific review. This process had revealed some problems with the first equation. The subsequent paper detailing the corrections and adjustments [652] had not been published and subject to peer review and comment.

Because of these concerns, the GDG (excluding the two researchers who left the room) felt unanimously that they were not able to recommend QRISK on the basis of the evidence available to them. They recommended to the Institute however that as the evidence in this area was rapidly changing the recommendation on risk score might need early review.

As the Institute did not wish to update a guideline so soon after publication, it was agreed with the GDG that publication be delayed while independent expert opinion was sought in regard to technical issues of concern to the GDG. With the agreement of the GDG, the Institute sought advice from experts independent of the groups that had derived either QRISK or modified the Framingham equations or guidelines that advocate them. Advice was sought from a:

i. Biostatistician:- Professor Doug Altman
ii. Epidemiologist: - Professor Sir Richard Peto FRS
iii. Expert in Cardiovascular Risk Estimation: Professor Rod Jackson

Their reviews are attached as an appendix.

The GDG reconvened in January 2008 to discuss the now published QRISK paper[652] and the independent reviews. The GDG discussed the independent reviews and sought clarification of some points from the two QRISK researchers who were GDG members. The GDG addressed methods for dealing with missing data, calibration and discrimination statistics for QRISK and the applicability and use of QRISK in different clinical settings.

The GDG had some outstanding concerns:

1. The calculation of the additional risk of some ethnic groups, in particular those of south Asian background.

The QRISK equation does not include a variable for ethnicity, but does include a variable for deprivation and family history. The previous recommended increase of a factor of 1.4 in risk for South Asian males when using the Framingham equation would overestimate the risk using the QRISK equation. As there is no information currently available on what, if any, increase would be appropriate for ethnicity, if ethnicity were accounted for, the GDG decided not to include any adjustment.

2. The management of patients who had previously been assessed with the Framingham equation and were currently on treatment. The GDG regarded it as inappropriate for a patient currently on treatment to be reassessed with the possibility of the treatment being stopped. The GDG agreed that patients already on treatment should not be reassessed using QRISK.

3. Accessibility of QRISK

The view of the GDG was that QRISK must be freely available for incorporation into primary care management software and to secondary care clinicians for use in hospital. The GDG agreed to ask for a guarantee from the developers of QRISK that the algorithms will be freely available from their website prior to publication.

4. Updating the algorithms

A major advantage of QRISK is that it can be updated to, for example, reflect changes in the UK population, or to include more variables such as ethnicity and chronic kidney disease. However there must be strict version control, therefore the GDG recommends that NICE work with developers to co-ordinate updates in QRISK with the publication of updates of the guideline.

The GDG (excluding the two researchers who left the room) unanimously agreed that QRISK should be recommended noting that this decision would go to wider consultation. The GDG agreed that the recommendation of QRISK will also allow the score to be improved with the potential to include other variables and outcomes of interest.

This section of the guideline went out for a four week stakeholder consultation and the **GDG met for the final time in March 2008** to review stakeholder comments. The GDG recognised that the three independent experts consulted had recommended QRISK but stakeholders had taken a broader view and identified areas of concern. The areas of concern discussed by the GDG are not listed in any particular order.

1. Ascertainment

Concern was expressed by stakeholders and discussed by the GDG that the validation of QRISK against Framingham and ASSIGN had used outcomes as measured in general practice databases and in ONS statistics. Ascertainment is likely to be less certain than in cohort studies.

2. Accuracy of data recorded in datasets

Some stakeholders had expressed concern about quality of data in GP datasets. The GDG were not concerned about recording of risk factors as these are the readings practitioners will use in clinical practice. They agreed with concerns regarding accuracy of outcome data as above.

3. Independent validation of QRISK

The details of the QRISK equation have not yet been made available. The GDG understood that the QRISK research group had valid reasons for this but were concerned that the current lack of availability means that independent validation and comparison with other scores has not yet been possible. This had made it difficult for stakeholders to examine validation. One group submitted an unpublished paper, where they had tried to derive the QRISK equation and replicate the QRISK validation papers. There were some major differences between their results and the QRISK validation papers. The GDG recognised the limitations of the paper in that it was not peer reviewed or published and they did not have the correct equation. However the paper highlighted the difficulties in comparing scores at this time.

4. Validation of QRISK other than in general practice records

The GDG agreed that ideally QRISK should be validated in clinical datasets as well as in databases for the reasons already discussed.

5. Use in practice

The GDG continued to have concerns about the practical use of QRISK in all health care settings. The GDG were not aware of any use of QRISK in clinical settings while clinicians have experience of use of Framingham.

6. Comparisons of ASSIGN and QRISK in the UK populations

A cogent case was made by the ASSIGN research group suggesting that overall the differences between Framingham, ASSIGN and QRISK were extremely similar in terms of discrimination. Neither the GDG nor the independent experts had compared QRISK to ASSIGN. Both ASSIGN and QRISK are

relatively new scores. ASSIGN could not currently be used in the UK population other than Scotland but a version of ASSIGN using a different, England and Wales appropriate, index of deprivation could be developed. The GDG did not think that they had enough evidence to decide that QRISK was the definitively better score for the UK over ASSIGN.

7. Overestimation of risk versus underestimation of risk

The available evidence indicates that Framingham overestimates risk in a UK population and QRISK underestimates risk. The GDG were less concerned about overestimating risk as interventions are known to have benefit below the thresholds currently used.

Final Decision

The GDG could not on the basis of the evidence or expertise before them make a decision that one risk assessment equation was clearly superior in the UK population.

The GDG debated the following in reaching their decision.

- *Should no equation be recommended as no one was definitively superior?*
  The GDG considered that if they did not give definitive guidance there may be a perception that risk assessment was not important. The evidence is clear that any structured assessment is superior to clinical judgement in assessing risk and enabling high risk people to access treatment. It would also not be in the interest of patients to potentially be assessed by different scores. This confusion could well lead to poorer uptake of treatment. All risk equations are blunt instruments which should be used in clinical practice as the starting point for a discussion between clinicians and patients and excessive emphasis on which risk score better estimates CVD risk for the individual patient obscures the primary importance of undertaking a structured risk assessment.
- *Was the uncertainty associated with adopting a new CVD risk score estimation equation acceptable?*
  The GDG recognised that there is a strong case for the use of a risk equation developed and validated on a UK population and takes account of deprivation. There were however concerns about QRISK within the GDG and the wider community as evidenced by stakeholder comments. The Framingham equations are currently the most widely used and understood. Recommending a different score required a higher level of certainty than the GDG had with regard to QRISK.

The GDG then voted (the secondary prevention expert left the room for part of the discussion and for the vote). Seven members were in favour of recommending risk assessment based on the Framingham equation with adaptations. One member voted in favour of recommending an equation based on UK data. One member abstained.

Conclusion

The GDG's decision was that Framingham despite its known limitations is currently in use and its limitations understood. Therefore there needs to be great confidence that the introduction of a new model will bring greater benefits. As QRISK is still a model in evolution, they were not certain that this was currently the case. The large confidence intervals with both models mean that either model will largely identify the same proportion of patients. The limitations of Framingham (e.g. over prediction, equity, other risk factors) are addressed in the recommendations.

GDG members had the opportunity to read and comment on the narrative, describing how the GDG came to its decision regarding choice of risk score, after the final meeting and the majority regarded this as an accurate representation of the decision. The QRISK researchers who had not been present for all of the discussion pointed out that the current underestimation of risk by QRISK in the THIN database was related to poor recording of family history and that the implementation of QRISK would increase the recording of this.

An issue of importance remains the implication of choice of risk score for vulnerable groups. The recommendation to use Framingham does not address issues of equity and people from an under deprived background remain less likely to be considered >20% risk. The recommendations include advice to adjust the Framingham score for ethnicity, family history and socioeconomic status. There is some evidence on how the Framingham score should be adjusted for ethnicity and family history but further validation of these adjustments is required. There is no direct evidence as to how it should be adjusted for socioeconomic status. QRISK does include socioeconomic status and family history but it is not known whether additional adjustment is required for ethnicity.

A research recommendation has been added to this guideline on further validation of all available risk scores in the UK population, on feasibility of using scores in different settings and the added value of including additional variables in risk scores.

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Following the publication of the guideline two further papers addressing QRISK validation were published. A paper comparing QRISK 2 and adjusted Framingham equations was published in 2008 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008; 336: p332) and in 2009 an independent evaluation of QRISK1 was published (Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ 2009;339:p2584).

Members of the guideline development group were consulted as to whether an update was appropriate but there was no consensus. NICE's Guidance Executive considered this feedback and came to the view that, although the evidence has moved on, an update was not appropriate as it did not seem that a clear conclusion would be reached favouring one method over another. In these circumstances the decision was taken by Guidance Executive in February 2010 to withdraw the guidance relating to a particular method of estimation so that the decision could be left to the healthcare practitioners to use the method best suited to their requirements.

Q.24 Methods of delivering tools for risk estimation to clinicians

- **Clinical effectiveness narrative**

A systematic review has examined methods to aid the healthcare professional in reporting cardiovascular risk score[175] (Appendix K). Only two studies were identified; one in people with a diagnosis of diabetes and the second in people diagnosed with hypertension.

The first study compared the documentation of the cardiovascular risk score at the front of the patient's notes with no documentation at the front of the notes in the control group.[609] For both the intervention and the control group the physicians were given standard information on weight, haemoglobin, microalbuninaria and cholesterol. At 6-month follow-up, treatment with antihypertensives and lipid lowering drugs was increased in the group with clearly identified risk scoring. However, this was only significant in patients at greater cardiovascular risk (> 20% 5-year risk) compared with those at lower risk (≤ 20% 5-year risk).

The second study, in people with hypertension, compared the use of the Framingham-Anderson 1991 risk calculation with an estimation of cardiovascular risk by a physician.[615] The physician in the intervention group was told the estimated risk calculation, while the control group had their risk estimated by a physician using clinical judgment. At eight-week follow-up, there was no benefit for inclusion of Framingham-Alderson 1991 10-year CVD risk in the therapeutic strategy. There was no difference between the groups in change in systolic and diastolic pressure or in change in prescription of antihypertensives. Concordance between the Framingham-Alderson 1991 calculated risk and the estimated risk by the physician was 35%.

A limitation to the methodological quality of the two studies is that they did not describe the method of randomisation, blinding or power calculation. As such the results of these studies should be interpreted with caution.[609,615]

Q.24.1 Cost-effectiveness narrative

There were no cost-effectiveness studies found surrounding the most effective method of providing tools for risk estimation to people at high risk of developing CVD.

Q.25 Lipid measurement

Q.25.1 Introduction

HDL cholesterol is an independent predictor of cardiovascular risk, high levels being 'protective' and lower levels of HDL cholesterol are associated with increased risk. The inclusion of the total/ HDL cholesterol ratio as a component of risk estimation has a substantial impact compared with the use of total cholesterol alone. A person with a total cholesterol of 5.2mmol/l and an HDL cholesterol of 0.7mmol/l has a ratio of 7.4 which confers a greater CVD risk than someone with a total cholesterol of 8mmol/l and an HDL cholesterol of 1.6mmol/l who has a ratio of 5.0. The ratio of total cholesterol/HDL cholesterol has been shown to be the optimal predictor of CVD risk when incorporated in multiple risk factor equations.[586]

The GDG also considered the number of pre-treatment readings, the utility of a fasting lipid profile prior to treatment and the time in which treatment should usually be initiated. Concern has been expressed about the lack of laboratory standardisation for lipid measurement.

Q.25.2 Evidence statements for lipid measurement

Both HDL cholesterol and total cholesterol form integral aspects of the Framingham, QRISK and ASSIGN equations. Management decisions should use both parameters as they are known to make independent contributions to CVD risk. Total and HDL cholesterol can be measured in non-fasting specimens.
Estimation of LDL cholesterol requires a fasting specimen which gives total cholesterol, HDL cholesterol and triglycerides. The LDLcholesterol is then calculated using the Friedewald equation. Currently available direct methods are inadequately standardised and validated and cannot be recommended)
Once an individual has had their risk factors measured and is found to be in a high- risk group for which active management is recommended, it may require several consultations and some time may be necessary for this information to be conveyed and assimilated and other clinical issues addressed. It would normally be expected that these issues would be dealt with and appropriate treatment started within 6 months of full risk factor assessment.

Individuals who are identified from their history or clinical findings to be at high increased risk of premature cardiovascular disease due to familial or other genetic factors require full investigation and/or specialist review. These people will include those with familial hypercholesterolaemia or monogenic lipid disorders.

Q.25.3 Measurement of lipid parameters for risk assessment

Framingham takes account of the ratio of total to HDL cholesterol in estimating risk. The ratio of the total cholesterol to HDL cholesterol is a better predictor of risk than either measure alone.[590,999]

The Heath Survey for England found that the mean HDL cholesterol level in men in England is 1.4 mmol/l, and in women it is 1.6 mmol/l. HDL cholesterol for women across all age ranges was higher than that for men.
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712

HDL cholesterol estimation is now widely available in laboratories. For clinical estimation of cardiovascular risk both total and HDL cholesterol should be measured. A non-fasting specimen is sufficient.

Where prior estimation of total or HDL cholesterol is not available, then values based on the average in Health Survey for England (2003), as above are appropriate.

Q.25.3.1 Accuracy of taking one reading of lipid levels versus taking repeated readings of lipid levels

Framingham risk estimates were based on a single measurement of total and HDL cholesterol and for risk estimation a single reading is sufficient.

Variability of measurement due to physiological variation, laboratory variation and statistical variation are discussed below.

Q.25.3.2 Accuracy of cholesterol measurement

Measured cholesterol levels incorporate an error term based on the coefficient of variation which, from published studies, is 7.2% for total cholesterol and 7.5% for HDL cholesterol.[1012] This error term results from day-to-day physiological variation, from laboratory variation or sample processing and from random variation. Laboratory variation has been a subject of concern and in the USA, and a national quality standard has been established for lipid assay.[1410] The GDG notes that there are concerns, particularly for HDL cholesterol, that no such standardisation exists in the UK.

Because of this individual variation in a single lipid measurement, repeated measurement will give greater precision. Precision is proportional to the square root of the sample size.[1329] Typically, someone who has a (true) long-term average total cholesterol level of 4.00 mmol/l will, on any given day, tend to have a measured level that differs by anywhere up to about 0.56 mmol/l (i.e., the within-person standard deviation is about 0.28 mmol/l). Thus, measured total cholesterol for such a person would be expected to lie somewhere between about 3.44 and 4.56 mmol/l based on a single measurement. In order to ensure that an individual had a 90% chance of having a genuine total cholesterol level below 4.00 mmol/l, this would require cholesterol to be lowered to 3.67 mmol/l based on one reading, to a mean of 3.76 mmol/l based on two readings and 3.80 mmol/l based on an average of 3 readings.

In routine practice clinicians find that performing serial replicate reading is not feasible and often base monitoring on one measurement and treatment decisions on two lipid measurements, accepting the imprecision. Where cholesterol levels are used to monitor or guide treatment, the selection of people for optimal treatment on the basis of a single reading is therefore somewhat

arbitrary.[1423] Some people below the treatment threshold on a particular day may be denied treatment following a single measurement below their 'true' level and in others treatment may be inappropriately given following a single reading above their 'true' level.

Q.25.3.3 The need for a fasting lipid measurement before starting treatment

There was no substantive evidence to support the view that a fasting specimen is advantageous before starting treatment. It was considered by the GDG that many clinicians view LDL cholesterol and triglycerides as an important adjunct to clinical management because they may inform diagnosis and are a baseline against which the progress and effectiveness of treatment can be judged. The GDG agreed that patients should have at least one fasting lipid measurement performed.

After an acute coronary event, there is an acute phase fall in LDL cholesterol and in HDL cholesterol and potential underestimate of pre-treatment levels. Measurement at this time is not advised. The GDG agreed that in people who have recently experienced an acute coronary event treatment should not be delayed but measurement can be delayed to 3 months after the event.[272,1180]

Q.25.3.4 Waiting time between initial assessment and further measurement of risk factors

The practicalities of several clinic attendances to assess and discuss risk and deal with other risk factors or clinical issues may take some time. However, the GDG felt that further delay in commencing treatment should be avoided and that most people wishing to have appropriate treatment should be started within 6 months of assessment.

Q.25.3.5 Patients with lipid disorders needing specialist assessment and management

People in whom familial hypercholesterolaemia or other monogenic familial disorders are suspected should be considered for further investigationand/or specialist review.

People with severe hyperlipidaemias should be considered for further investigation and/or specialist review.

The management of familial lipid disorders will be the subject to the forthcoming NICE guideline: Familial hypercholaesterolemia: identification and management (2008).

Amended March 2010 Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

- **Cost-effectiveness narrative**

There were no cost effectiveness studies found surrounding the measurement of lipid parameters for risk assessment.

Q.26 Lifestyle modifications for the primary and secondary prevention of CVD

Q.27 Recommendations

Cardioprotective diet recommendations

27. People at high risk of or with CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of

dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by monounsaturated and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice.

28. **People at high risk of or with CVD should be advised to eat at least five portions of fruit and vegetables per day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk**

29. **People at high risk of or with CVD should be advised to consume at least two portions of fish per week, including a portion of oily fish. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet**

30. **Pregnant women should be advised to limit their oily fish to no more than two portions per week. Further information and advice on oily fish consumption can be found at www.eatwell.gov.uk/healthydiet**

31. **People should not routinely be recommended to take omega-3 fatty acid supplements for the primary prevention of CVD.**

Plant stanols and sterols recommendations

32. **People should not routinely be recommended to take plant sterols and stanols for the primary prevention of CVD.**

Q.28 Cardioprotective dietary advice

Q.28.1 Evidence statements for cardioprotective dietary advice

Low fat diet
No randomised controlled trials were identified in people at high risk of CVD that compared low fat diet with usual diet for the outcomes mortality or morbidity.
One small randomised controlled trial in people at high risk of CVD with elevated cholesterol and triglycerides found that advice to reduce consumption of fat, sugar and alcohol was associated with reduction in total cholesterol and fasting triglycerides compared with control.
In patients with suspected CHD, one small randomised controlled trial found that adopting a lipid–lowering diet reduced total cardiac events compared to usual care but did not confer any benefit for the outcomes of cardiovascular mortality, MI, stroke, coronary surgery or angioplasty. Lipid–lowering diet was associated with decreased total and LDL cholesterol compared to baseline levels.
No randomised controlled trials were identified that compared low fat diet with usual diet in patients with peripheral arterial disease or following stroke.
Increased fruit and vegetable diet
No randomised controlled trials were identified that compared increased fruit and vegetables diet

with usual diet in people at high risk of CVD.
One randomised controlled trial in patients with angina found that advice to increase consumption of fruit and vegetables was not associated with a reduction in all cause mortality, cardiac death or sudden death compared with advice to eat sensibly.
No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in patients with peripheral arterial disease or following stroke.
One randomised controlled trial in patients with angina found that advice to eat oily fish or take omega 3 fatty acid supplements was not associated with a reduction all cause mortality or cardiac death.
One randomised controlled trial in hypercholesterolemic people without and with coronary artery disease found that omega 3 fatty acid supplements was associated with a reduction in the primary outcome of any major cardiovascular event, and the secondary outcomes of unstable angina and non fatal coronary events (HR 0.81, 95%CI 0.68 to 0.96)

Q.29 Clinical effectiveness of low fat diets for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of low fat diet versus no change in diet for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

One small randomised controlled trial was identified on the effectiveness of low fat diet versus no change in diet to modify lipid profiles in people at high risk of CVD.[658]

The participants in this trial were a sub-sample from a population of 1232 men aged 40-49 years selected for a previous study[660] according to the following criteria: mean serum cholesterol = 7.5 to 9.8 mmol/l, coronary risk scores (based on cholesterol, smoking and BP) in the upper quartile of the distribution and systolic BP < 150 mmHg. The sub-sample of 104 men were further selected for this trial[658] if fasting triglycerides > 2.5 mmol/l.

A total of 104 men were randomised to either the intervention group which received dietary advice over a five year period or to the control who received no advice.

Participants in the dietary intervention group were given advice to reduce total energy intake (mainly by reducing sugar, alcohol and fat), reduce saturated fat consumption and slightly increase polyunsaturated fat consumption. Participants in the intervention group also received anti-smoking advice.

After five years, the dietary intervention was found to be associated with a reduction in total cholesterol (-10.5%, 95% CI -1.5% to -11.7%) and fasting triglycerides (- 27.2, 95% CI -0.1% to -27.4%) compared with control.[658]

Q.29.1 Evidence into recommendations

Due to the lack of clinical outcome data in this trial, its small size and problems with generalisibility, it was decided by the GDG that it should be excluded and that recommendations made in the Joint British Societies' guidelines on prevention of CVD in clinical practice[1445] would be adopted (total fat intake should be ≤ 30% of total energy intake and saturated fats should comprise ≤ 10% of total energy intake). These targets are slightly lower for total fat than those set by the Department of

Heath for the general population (total fat ≤ 35% of total energy intake and saturated fats ≤ 10% of total energy intake).[421]

Q.29.2 Clinical effectiveness of low fat diets for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD that compared advice to adopt a low fat diet with no dietary advice.[1417] This trial recruited men referred for coronary angioplasty to investigate angina pectoris, or other findings suggestive of coronary heart disease (CHD) (70% with angina, 45% with a history of MI). A total of 90 participants were randomised to one of three groups; usual care, lipid-lowering diet, or lipid-lowering diet plus cholestyramine therapy. Patients in the lipid–lowering diet and lipid–lowering diet plus cholestyramine therapy groups were given the following advice by a dietician: to reduce total fat intake to 27% of dietary energy, to reduce saturated fat intake to 8-10% of dietary energy, to reduce dietary cholesterol to 100 mg / 1000 kcal, to increase omega 3 and 6 fatty acid intake to 8% of dietary energy, and to increase fibre intake. Participants were followed up for a mean duration of 39 months.

Lipid–lowering diet did not confer any benefit over usual care for the outcomes of cardiovascular death, MI, coronary surgery, angioplasty or stroke. Lipid–lowering diet did, however, reduce total cardiac events compared with usual care 10/28 (36%) lipid-lowering diet versus 3/27 (11%) usual care) ($P < 0.05$)) and improve the severity of angina symptoms ($P < 0.01$ lipid-lowering diet versus usual care). Participants in the lipid-lowering diet group had lower total and LDL cholesterol levels at the end of the trial (39 months) compared with their baseline levels ($P < 0.01$), while there was no change in HDL cholesterol.[1417]

Q.29.3 Evidence into recommendations

This randomised controlled trial recruited small numbers and was the only trial identified in patients with angina, stroke or peripheral arterial disease. The GDG decided to adopt recommendations made in the Joint British Societies' guidelines on prevention of CVD in clinical practice[1445] which recommends that total fat intake should be 30% or less of total energy intake and saturated fats should comprise 10% or less of total energy intake. These targets are slightly lower for total fat than those set by the Department of Heath for the general population (total fat ≤ 35% of total energy intake and saturated fats ≤ 10% of total energy intake).[421]

Q.29.4 Clinical effectiveness of increased fruit and vegetables diet for the primary prevention of CVD

No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in people at high risk of CVD.

Q.29.5 Evidence into recommendations

The GDG decided to recommend five portions of fruit and vegetables per day in line with advice given to the general population. For further information, please refer to the Department of Health's website: 5aday.nhs.uk, and the Food Standards Agency website: www.eatwell.gov.uk/healthydiet/.

Q.29.6 Clinical effectiveness of increased fruit and vegetables diet for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD that compared advice to increase fruit and vegetables versus non specific dietary advice.[251] This trial recruited men under the age of 70 who were being treated for angina (50% also had a prior MI). Recruitment

occurred in two phases: Phase I was between 1990 and 1992 and phase II between 1993 and 1996, follow up was in 1999. A total of 3114 participants were randomised to one of four groups:

1. Advice to eat at least 2 portions of oily fish per week or take up to 3 'MaxEPA' fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA) as a partial or total substitute. In the first phase of the study, participants chose diet or capsules or a mixture, in the second phase, participants were sub randomised to receive dietary advice or fish oil capsules.
2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange juice daily and to increase intake of soluble fibre in the form of oats.
3. A combination of 1. and 2.
4. 'Sensible eating' – non-specific advice that did not include either of the above interventions.

Advice to increase consumption of fruit and vegetables was found to be poorly complied with and the advice did not confer any benefit on mortality (all deaths, cardiac deaths and sudden deaths) compared with 'sensible eating'.

Q.29.7 Evidence into recommendations

Only one randomised controlled trial found on the effectiveness of an increased fruit and vegetables diet in patients with angina[251] and no randomised controlled trials were identified in patients with peripheral arterial disease or following stroke. The GDG decided to recommend five portions of fruit and vegetables per day in line with advice given to the general population. For further information, please refer to the Department of Health paper 'Choosing a Better Diet: a food and health action plan'[421], the Department of Health's website: 5aday.nhs.uk, the COMA report 'Nutritional Aspects of Cardiovascular Disease'[395] and the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/)[46]

Q.29.8 Clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the primary prevention of CVD

One randomised controlled trial was identified that examined the effect of omega 3 fatty acid supplements in Japanese hypercholesterolaemia patients (18 645) without and with coronary artery disease (26% of the total number of recruits in the study, of which 21% had a prior history of MI, 61% had angina and 18% were recruited following revascularisation).[1466] Patients in the intervention group were given omega 3 fatty acid supplements (1800 mg / day) plus a statin, either pravastatin (average dose 10 mg /day) or simvastatin (5.6 mg / day). Patients in the control group received a statin alone, either pravastatin (average dose 10 mg / day) or simvastatin (5.6 mg / day). At a mean follow up of 4.6 years and for patients with and without coronary artery disease, omega 3 fatty acid supplementation was associated with a reduction in the primary outcome of any major coronary event (including sudden death, fatal and non fatal MI, unstable angina, angioplasty, stenting and CABG) (HR 0.81, 95%CI 0.69 to 0.95). Omega 3 fatty acid supplementation was associated with a reduction in the secondary outcomes of unstable angina (HR 0.76, 95%CI 0.62 to 0.95) and non fatal coronary events (HR 0.81, 95%CI 0.68 to 0.96) Omega 3 fatty acid supplementation did not confer any benefit compared with no supplementation for the following secondary outcomes; sudden death, fatal MI, non fatal MI, CABG or PTCA, coronary death or MI, fatal MI or non fatal MI, and coronary death.[1466]

Analysis of the results for patients without coronary artery disease found that omega 3 fatty acid supplementation had no effect on the primary outcome, or any of the secondary outcomes compared with no supplementation. Analysis of the results of omega 3 fatty acid supplementation in the patients with coronary artery disease for the primary outcome of any major coronary event gave a hazard ratio of 0.82 (95%CI 0.657 to 0.998) compared with no supplementation. Unstable angina was reduced in the coronary artery disease population allocated to omega 3 supplementation unstable angina (HR 0.72, 95%CI 0.55 to 0.95).[1466]

Q.29.9 Evidence into recommendations

The GDG considered that for dietary fish, the recommendations made by the Joint British Societies' guidelines on prevention of CVD in clinical practice[1445] should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation for people at high risk of CVD.

Q.29.10 Clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the secondary prevention of CVD

One randomised controlled trial was identified in patients with a history of CVD which compared increased consumption of oily fish or taking omega 3 fatty acid supplements versus no change in diet.[251] This trial has previously been described in the section on clinical effectiveness of increased fruit and vegetables diet for the secondary prevention of CVD. Trial participants were men under the age of 70 who were being treated for angina (50% also had a prior MI). A total of 3114 participants were randomised to one of four groups:

1. Advice to eat at least 2 portions of oily fish per week or take up to 3 'MaxEPA' fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA) as a partial or total substitute. In the first phase of the study, participants chose diet or capsules or a mixture, in the second phase, participants were sub randomised to receive dietary advice or fish oil capsules.
2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange juice daily and to increase intake of soluble fibre in the form of oats.
3. A combination of 1. and 2.
4. 'Sensible eating' – non-specific advice that did not include either of the above interventions.

Four way analysis found that advice to eat oily fish or take supplements was not associated with a significant change in total number of deaths, number of cardiac deaths or number of sudden deaths compared with the control group who were told to 'eat sensibly'.

Two way analysis comparing 'all fish advice' (intervention groups 1 and 3) with 'no fish advice' (intervention group 2 and control group 4) found that advice to eat oily fish or take supplements was not associated with a change in the total number of deaths but was associated with an increase in the number of cardiac deaths (11.5% 'all fish advice' versus 9.0% 'no fish advice', P = 0.02) and number of sudden deaths (4.6% 'all fish advice' versus 3% 'no fish advice', P = 0.02).

Adjusted hazard ratios were calculated for 'all fish advice' (intervention groups 1 and 3) compared to 'no fish advice' (intervention group 2 and control group 4). 'All fish advice' was found to be associated with an increase in the risk of sudden death (HR 1.54, 95% CI 1.06 to 2.23) compared with 'no fish advice' but no change was observed for total or cardiac mortality.

A subgroup analysis was performed and adjusted hazard ratios were calculated separately for those given fish advice (intervention groups 1 and 3) who were sub-randomised to receive omega 3 fatty acid supplements (a subset of 462 patients were sub-randomised to this treatment during the second phase of recruitment) and all others given 'fish advice' who were not sub randomised (n = 1109) compared with 'no fish advice' (intervention group 2 and control group 4). It was found that those sub randomised to receive omega 3 fatty acid supplements during the second phase of the trial had an increased risk of cardiac death (HR 1.45, 95% CI 1.05 to 1.99) and sudden death (HR 1.84, 95% CI 1.11 to 3.05) compared with those randomised to receive 'no fish advice' throughout the trial. All other participants who received 'fish advice' (intervention groups 1 and 3) but were not sub randomised to receive supplements were not found to have an increased risk of total mortality, cardiac mortality or sudden death compared with 'no fish advice'. It should be noted that this was a

post hoc subgroup analysis, and the results should be interpreted with caution because the patient numbers in the analysis indicate that the analysis is statistically underpowered.

A second randomised controlled trial was identified that examined the effect of omega 3 fatty acid supplements in Japanese hypercholesterolaemia patients (18 645) without and with coronary artery disease. Patients with coronary artery disease accounted for 26% of the total number of participants in the study, and 21% had a prior history of MI, 61% had angina and 18% were recruited following revascularisation).[1466] This study has been described in the section on clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation) for the primary prevention of CVD. Patients in the intervention group were given omega 3 fatty acid supplements (1800 mg / day) plus a statin either pravastatin (average dose 10 mg /day) or simvastatin (5.6 mg / day). Patients in the control group received a statin alone, either pravastatin (average dose 10 mg / day) or simvastatin (5.6 mg / day). Analysis of the results of omega 3 fatty acid supplementation in the patients with coronary artery disease for the primary outcome of any major coronary event gave a hazard ratio of 0.82 (95%CI 0.657 to 0.998) compared with no supplementation. Unstable angina was reduced in the coronary artery disease population allocated to omega 3 supplementation unstable angina (HR 0.72, 95%CI 0.55 to 0.95).

Q.29.11 Evidence into recommendations

Due to the conflicting results of the two studies described for oily fish consumption / omega 3 fatty acid supplementation[251,1466], and the lack of evidence for patients with peripheral arterial disease or following stroke, the GDG considered that for dietary fish, the recommendations made by the Joint British Societies' guidelines on prevention of CVD in clinical practice (2005)[1445] should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation in patients with angina, peripheral arterial disease or stroke.

Q.30 Plant stanols and sterols

Q.30.1 Evidence statements for plants stanols and sterols

No randomised controlled trials were identified in people at high risk of CVD that compared giving plant stanols and sterols with usual diet for the outcomes of mortality or morbidity.
No randomised controlled trials with cardiovascular endpoints were identified that compared giving plant stanols or sterols with usual diet in patients with CVD

Q.30.2 Evidence into recommendations

No randomised controlled trials were identified which examined the effectiveness of plant stanols and sterols in primary and secondary prevention with respect to cardiovascular outcomes. The GDG therefore decided that there was insufficient evidence to recommend their use.

Q.31 Drug therapy for the primary prevention of cardiovascular disease (CVD)

Q.31.1 Recommendations for drug therapy

33. When considering lipid modification therapy in primary and secondary prevention, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

Drug therapy for primary prevention

34. Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- **smoking status**
- **alcohol consumption**
- **blood pressure (see 'Hypertension', NICE clinical guideline 34)**
- **body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)**
- **fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)**
- **fasting blood glucose**
- **renal function**
- **liver function (transaminases)**
- **thyroid-stimulating hormone (TSH) if dyslipidaemia is present.**

Statins for primary prevention

35. Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).

36. The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.17

37. If statin treatment is appropriate, it should be offered as soon as practicable after a full risk factor assessment.

38. When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).17

39.Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

40.Higher intensity statins should not routinely be offered to people for the primary prevention of CVD.

41.A target for total or LDL cholesterol is not recommended for people who are treated with a statin for primary prevention of CVD.

42.Once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy and whether to review the lipid profile.

Fibrates for primary prevention

43.Fibrates should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, fibrates may be considered.

Nicotinic acid for primary prevention

44.Nicotinic acid should not be offered for the primary prevention of CVD.

Anion exchange resins for primary prevention

45.Anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, an anion exchange resin may be considered.

Combination therapy for primary prevention

46.The combination of an anion exchange resin, fibrate or nicotinic acid with a statin should not be offered for the primary prevention of CVD.

47.The combination of a fish oil supplement with a statin should not be offered for the primary prevention of CVD.

Monitoring of statin treatment for primary and secondary prevention

48.If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it.

49. People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured.

50. Creatine kinase should not be routinely monitored in asymptomatic people who are being treated with a statin.

51. Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

52. People who have liver enzymes (transaminases) that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.

53. If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought.

Q.32 Introduction to drug therapy for the primary prevention of CVD

This chapter considers pharmacological treatments for people whose 10 year risk of developing CVD is greater than 20% but who have not yet experienced an event. People with diabetes or familial lipid disorders are excluded from these recommendations and are considered in alternative NICE guidance.

Statins are the drug of first choice for the primary prevention of CVD as they are more effective at lowering LDL cholesterol than other drugs currently licensed for primary prevention and have been shown to have a greater impact on clinical outcome.

The NICE Technology Appraisal [1007] has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost effectiveness of statins and our recommendations on the initiation of statin therapy are based upon this report.

The NICE Technology Appraisal recommends statin therapy as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This may result in more than half of the men aged over 50 years and 20% of the women over 65 years being considered for lipid lowering therapy.

The routine use of higher intensity statins has not been recommended for primary prevention. Neither has this guideline recommended the use of cholesterol targets for primary prevention. Treatment targets are considered further in the secondary prevention drug therapy chapter.

This guideline has not made a detailed study of the safety of statins which is the proper concern of other regulatory agencies but has considered evidence from one systematic review and two meta-analyses of statin safety. Statins are generally well tolerated and the occurrences of serious adverse events are rare especially at the doses used for primary prevention.

Before the licensing of statins, fibrates were one of the mainstays of lipid modification, usually for people with established CVD. Their use for primary prevention was controversial and the failure to demonstrate reductions in total mortality in the 1978 cooperative World Health Organisation primary prevention trial [1449] and the 1987 Helsinki Heart Study [516] led to concerns about the effectiveness of fibrates.

Anion exchange resins were also used as first line agents for the management of dyslipidaemia and in secondary prevention before the advent of statins. The 1984 Lipid Research Clinics coronary primary

prevention trial[8,9] was an early trial of effectiveness with significant reductions in cardiovascular endpoints but no significant difference in total mortality.

In the last 20 years little further progress has been made on randomised trials with cardiovascular outcomes testing the effectiveness of fibrates or anion exchange resins for primary prevention.

Q.33 Statins

Q.33.1 Evidence statements for statins

Statin therapy
For people without clinical evidence of CVD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of fatal MI and nonfatal MI and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo.
For people without clinical evidence of CHD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality, fatal MI, nonfatal MI and stable angina and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo.
No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD.
The NICE Statin TA94, concluded that statin treatment in patients with CVD is cost effective compared with no statin treatment (NICE Technology Appraisal guidance, 'Statins for the prevention of cardiovascular events' TA 94, 2006)[1007].
Adverse events
In a systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports, the incidence of major adverse events associated with skeletal muscle and the liver was low.
Incidence of rhabdomyolysis was estimated at 3.4 per 100,000 person years (this rose to 4.2 per 100,000 person years in patients treated with statins which are metabolised by cytochrome P450 3A4 and was ten fold higher when a statin was combined with gemfibrozil).
Statin therapy was not found to be associated with a significant increase in the incidence of raised creatine kinase. Incidence of myopathy was estimated at 11 per 100,000 person years and incidence of peripheral neuropathy was estimated at 12 per 100,000 person years.
Elevations of the liver enzymes alanine aminotransferase and / or aspartate aminotransferase were reported more frequently in those treated with statins compared with placebo, especially at higher doses. Trials showed no excess of liver disease or chronic kidneyl disease in statin allocated participants.
A meta-analysis of data from 18 randomised controlled trials found statin therapy to be associated with a greater odds of any adverse event compared with placebo. A number needed to harm (NNH) analysis was performed and compared to placebo the number of people that would need to be treated with a statin to observe any statin-related adverse event was197 people, to observe a statin-related rhabdomyolysis was 7,428 people and to observe statin-related rhabdomyolysis or creatine

kinase > 10 x upper limit of normal was 3,400 people.
A meta-analysis of 26 randomised controlled trials showed cancer incidence and cancer death to be unaffected by statin therapy. A subgroup analysis by cancer type also found no effect of statin therapy.

Q.33.2 Clinical effectiveness of statins

Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the 'line of no effect' i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal entitled 'Statins for the prevention of cardiovascular events' 2006[1007] states that:

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

The recommendation was based upon assessment of the effectiveness of statin therapy in people without clinical evidence of CVD at study entry and in people without clinical evidence of coronary heart disease (CHD) at study entry (some or all of whom had other CVD at study entry).

Two randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CVD at study entry; CAIUS [955] and CARDS [330], and a further three randomised controlled trials were identified that presented subgroup analyses for people without CVD; ASCOT-LLA [1233], PROSPER [1247] and WOSCOPS [1249].

A meta-analysis was conducted that included data from three of these trials, two of which used pravastatin 40 mg; CAIUS [955] and PROSPER [1247], and one used atorvastatin 10 mg; CARDS [330]. Subgroup data from the ASCOT-LLA [1233] and WOSCOPS [1249] trials was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a reduction in the risk of fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.60, 95% CI 0.37 to 0.97) and the composite outcomes of CHD death and nonfatal MI (RR 0.66, 95% CI 0.46 to 0.96) and of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.64, 95% CI 0.48 to 0.84). Statin therapy was not found to be associated with a reduction in the risk of the following outcomes; all cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, unstable angina and revascularisation [1007].

Four randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CHD at study entry; CAIUS [955], CARDS [330], DALI [432] and ASCOT-LLA [1233]. A further three randomised controlled trials were identified that presented subgroup analyses for people without CHD; PROSPER [1247], WOSCOPS [1249] and HPS[26].

A meta-analysis was conducted that included data from six of these trials, two of which used pravastatin 40 mg; CAIUS [955] and PROSPER [1247]. One used simvastatin 40 mg; HPS [26], and three used atorvastatin 10 mg; ASCOT-LLA [1233], CARDS [330], and DALI [432]. Subgroup data from the WOSCOPS trial was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality (RR 0.83, 95% CI 0.70 to 0.98), fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.58, 95% CI 0.36 to 0.94) and stable angina (RR 0.59, 95% CI 0.38 to 0.90) and the composite outcomes of CHD death and nonfatal MI (RR 0.64, 95% CI 0.50 to 0.82) and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.73, 95% CI 0.63 to 0.86). Statin therapy was not found to be associated with a reduction in the risk of the following outcomes: cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, PAD, unstable angina and revascularization [1007].

Results from the largest primary prevention study (n = 10,305) (ASCOT-LLA [1233], which compared atorvastatin with placebo over approximately 3 years, suggested that the number needed to treat (NNT) to avoid either a death from CHD or a nonfatal MI, in people without existing CHD, was 95 (95% CI 60 to 216).

The NICE Technology Appraisal also considered whether statins differ in their relative effectiveness in the following population subgroups: In women compared with men at a similar level of cardiovascular risk; in people with diabetes compared to people without diabetes; or in people aged over 65 years compared with people aged under 65 years. Evidence from placebo-controlled trials showed that statins do not differ in their relative effectiveness in these subgroups. No placebo-controlled trials were identified that provided information relating to people from different ethnic groups.

The NICE Technology Appraisal [1007] states further that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Cost effectiveness analysis indicates that simvastatin 40 mg and pravastatin 40 mg are both cost effective options for the primary prevention of CVD and the GDG considered that they were the most effective preparations at the lowest acquisition cost.

Q.33.3 High intensity versus standard intensity statin therapy

No randomised controlled trials were identified that included cardiovascular events and compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD. Higher intensity statin therapy is understood as statins, including simvastatin 80mg, whose effect on cholesterol lowering is greater than that of simvastatin 40mg. The GDG thus considered it was inappropriate to routinely recommend their use for the primary prevention of CVD.

Q.33.4 Cholesterol 'targets'

There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events. In addition, the clinical effectiveness of higher intensity statins and of combining statins with other lipid lowering drugs has yet to be demonstrated for primary prevention. It was decided that due to the lack of evidence, this guideline would not recommend the use of target levels of cholesterol for people at high risk of CVD. This is discussed further under the drug therapy secondary prevention.

Q.33.5 Adverse events associated with lower intensity statin therapy

Three papers were identified on the adverse events associated with lower intensity statin therapy. Two papers reviewed and meta-analysed all adverse events (especially those connected with skeletal muscle and the liver) [818 1256] and one examined statin usage and the risk of cancer [376].

It was noted by the GDG that there are limitations associated with these studies which may result in underestimation of adverse events. Firstly, all randomised controlled trials which have examined the effectiveness of statin therapy excluded some potential participants and a number of randomised controlled trials have also included a pre-randomisation run-in phase during which participants were treated with an open label statin. At the end of this time, some chose not to enter the trial or had some other reason not to do so. Thus, tolerability may be better and the incidences of adverse events lower in the trials than in unselected patients. Secondly, trials may not necessarily report all side effects that are experienced, although it is likely that serious side effects are reported. Thirdly,

the duration of randomised controlled trials may be shorter than the lag time expected for cancer manifestation.

The first study was a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports [818]. The incidence of rhabdomyolysis was estimated from the cohort studies: for statins other than cerivastatin was 3.4 (95% CI 1.6 to 6.5) per 100,000 person years, with a case fatality of 10%. The rates were about 10 times higher for cerivastatin and also for statins other than cerivastatin when taken with gemfibrozil. For cerivastatin taken with gemfibrozil, the incidence was 2,000 times higher, an absolute annual incidence of about 10%. Gemfibrozil increases the concentration of cerivastatin about 5-fold, which may be as a result of gemfibrozil-based inhibition of cerivastatin acid glucuronidation. Cerivastatin was withdrawn because of this unacceptable risk of serious side effects. In contrast there were no incidences of rhabdomyolysis with pravastatin or fluvastatin (not oxidised by CYP3A4) and the mean incidence of rhabdomyolysis among those taking lovastatin, simvastatin or atorvastatin (oxidised by cytochrome P450 3A4 (CYP3A4)) was 4.2 (95% CI 1.9 to 8.0) per 100,000 person years. This difference was not statistically significant because relatively few person-years of follow-up were recorded for fluvastatin and pravastatin.

The mean incidence of myopathy in patients treated with statins was 11 per 100,000 person years (estimated from cohort studies, supported by randomised trials). There was no significant difference in the incidence of a raised creatine kinase to ≥ 10 X ULN on a single measurement during routine monitoring between participants in 13 trials allocated to a statin compared to those allocated placebo (83 per 100,000 person years of statin treatment versus 60 per 100,000 person years with placebo). In two trials none had creatine kinase elevated on 2 consecutive measurements [818].

The incidence of liver disease attributable to statin therapy is rare. In 3 randomised trials of pravastatin, both gall bladder and hepatobiliary disorders were less common in patients allocated statins than in those allocated placebo. Elevations in alanine aminotransferase and or aspartate aminotransferase were reported more frequently in patients treated with statins than with placebo, and elevations of alanine aminotransferase (defined as ≥ 3 times the ULN, or 120 units/l) were found in 300 statin-allocated and 200 placebo-allocated participants per 100,000 person-years. However, statistical heterogeneity across the trials was noted. An elevated alanine aminotransferase on 2 consecutive measurements was found in 110 participants allocated to a statin and in 40 participants allocated to placebo per 100,000 person-years. Elevations in alanine aminotransferase were reported more frequently with higher doses of statin. The systematic review reported that in 100,000 person-years of statin use, denying 300 persons with elevated alanine aminotransferase the benefit of a statin (or 110 persons if repeat measures were used) would prevent liver disease in less than 1 person [818].

Randomised trials showed no excess of chronic kidney disease or proteinuria in statin allocated participants. There is evidence that statins cause peripheral neuropathy but the attributable risk is small (12 per 100,000 person years estimated from cohort studies and case reports). No change in cognitive function was found in trials of statins in elderly patients [818].

The second study was a meta-analysis [1256] which analysed data from 18 randomised controlled trials published in the last 11 years. The total number of participants randomised to receive a statin was 36 062 and to receive placebo was 35 046. Trials ranged in duration from 6 weeks to 317 weeks. Simvastatin or pravastatin comprised 85.8% of the cumulative statin exposure. Statin therapy was found to be associated with a greater odds of any adverse event that is not directly associated with cardiovascular disease compared with placebo (OR 1.17, 95% CI 1.06 to 1.28). A number needed to harm (NNH) analysis was also performed. The NNH (over 1 year) was 197 for any adverse event (which included myopathy-related events myalgia, myopathy or asthenia), creatine kinase elevation, elevated liver function tests > 3 x ULN or rhabdomyolysis), absolute risk was calculated at 0.51% (95% CI 0.29% to 0.73%). Thus 197 patients would need to be treated for 1 year for one adverse event. For

non-serious adverse events (excludes rhabdomyolysis and creatine kinase > 10 X ULN), the NNH was 209 people (over one year), absolute risk = 0.48% (95% CI 0.25% to 0.70%). Rhabdomyolysis was rare; the NNH was 7428 people (7428 people would have to be treated over 1 year for one event), and the absolute risk was 0.01% (95% CI -0.01% to 0.03%). The incidence of rhabdomyolysis or creatine kinase > 10 X ULN was also rare with a NNH of 3400 people and an absolute risk of 0.03% (95% CI -0.03% to 0.09%).

The third study was a meta-analysis [376] which examined statin usage and the risk of cancer. Twenty six randomised controlled trials were included (n = 86,936 participants). The number of participants ranged between 151 and 20,536 and the duration of patient follow-up for cancer ranged from 1.9 years to 10.4 years. Cancer incidence was found to be unaffected by statin therapy (OR 1.02, 95% CI 0.97 to 1.07), based on 20 studies, and cancer death was similarly unaffected (OR 1.01, 95% CI 0.93 to 1.09), based on 19 studies. A subgroup analysis by cancer type (breast, prostate, gastrointestinal, colon, respiratory and melanoma) was performed which also showed a neutral effect of statin therapy.

Q.33.6 Cost effectiveness of statins

The NICE Technology Appraisal [1007] states further that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Three further cost effectiveness analysis published after the TA were identified. Two of them compared pravastatin 40mg with placebo, Tonkin [1341], Nagata-Kobayashi [995] and concluded that pravastatin 40 mg is a cost effective option for the primary prevention of CVD especially for the high risk group. Nagata-Kobayashi [995] found that pravastatin 40 mg was not cost effective in low risk patients compared with placebo. The third study by Lindgren [851] compared atorvastatin 10 mg with placebo in the prevention of coronary and stroke events using data from the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering arm (ASCOT-LLA) [1233]. They found that Atorvastatin 10mg was cost effective with an estimated ICER of about £7349 per event avoided. There was an average of 97 events per 1000 patients in the treatment group at an additional cost of £260 per patient compared to 132 events per 1000 patients in the placebo group. The study was well conducted and used appropriate methodology. The findings were robust in sensitivity analysis. They provided a cost per life year gained in their discussion which is a better measure of cost effectiveness than the cost per event avoided they used in their main analysis.

In conclusion lower intensity statins are cost effective. Following the NICE Technology Appraisal [1007], statins with lowest acquisition cost should be used for treatment in primary prevention. The GDG based its recommendation not to recommend higher intensity statins for primary prevention on the lack of trial evidence of benefit from a reduction of cardiovascular events. A cost effectiveness analysis was therefore not considered appropriate. This decision was made on a majority basis.

Q.33.7 Evidence to recommendations – statins

The NICE Technology Appraisal [1007] review confirms that for primary prevention, statins are effective in reducing fatal and nonfatal MI and the composite outcome CHD death or nonfatal MI, fatal and nonfatal stroke and revascularisation. In trials predominantly comprising primary prevention but including a minority of people with established CVD, meta-analysis found that statin therapy was associated with a reduction in the risk of all cause mortality, fatal and nonfatal MI and the composite outcomes of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization. For primary prevention lower intensity statins are safe and cost-effective and there is trial evidence of cardiovascular benefit and low acquisition cost for simvastatin 40 mg and pravastatin 40 mg.

Q.34 Fibrates

Q.34.1 Evidence Statements for fibrates

One randomised controlled trial in men with elevated non-HDL cholesterol found that gemfibrozil therapy was associated with a reduction in the incidence of the combination of fatal and nonfatal MI and cardiac death compared with placebo. Gemfibrozil therapy was not associated with a reduction in total mortality compared with placebo.
One randomised controlled trial in men with elevated total cholesterol found that clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with placebo. Analysis of the individual components of this endpoint found that clofibrate therapy was associated with a reduction in nonfatal MI compared with placebo but not fatal ischaemic heart disease.
Clofibrate therapy was found to be associated with an increase in all cause mortality compared with placebo.

Q.34.2 Clinical effectiveness of fibrates

Two randomised controlled trials were identified that compared fibrate therapy with placebo in people at high risk of CVD [1449].

The first randomised controlled trial [1449] recruited healthy men aged 30 to 59 years on the basis of their serum cholesterol levels. A total of 15,745 participants were stratified according to their total cholesterol level and randomised to one of three groups (one intervention group and two control groups):

a) Intervention group: Men with a mean total cholesterol level of 6.45 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive clofibrate 1.6 g daily.
b) High cholesterol control group: Men with a mean total cholesterol level of 6.40 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).
c) Low cholesterol control group: Men with a mean total cholesterol level of 4.69 +/- 0.01 mmol/l chosen at random from the lowest third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).

The trial was conducted in three European centres: Prague, Budapest and Edinburgh and participants were followed up for 5 years. Clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with the high cholesterol control group (167/5331 group 1 versus 208/5296 group 2, $P < 0.05$). When the individual components of this endpoint were analysed separately, clofibrate therapy was found to be associated with a reduction in nonfatal MI (131/5331 group 1 versus 174/5296 group 2, $P < 0.05$) whereas no difference was found for the outcome of fatal ischaemic heart disease [1449].

Clofibrate therapy was found to be associated with an increase in all cause mortality compared with the high cholesterol control group (162/5331 group 1 versus 127/5296 group 2, $P < 0.05$). The results were also analysed separately by cause of death and clofibrate therapy was found to be associated with an increase in mortality from 'other medical causes' (16/5331 group 1 versus 5/5296 group 2, $P < 0.05$), 'all causes other than IHD' (108/5331 group 1 versus 79/5296 group 2, $P < 0.05$) and 'all

causes other than IHD, Vascular and Accidents and Violence' (77/5331 group 1 versus 47/5296 group 2, P < 0.01) compared with the high cholesterol control group. There was no difference in the numbers of deaths due to ischaemic heart disease, 'other vascular causes or accidents' and violence between groups 1 and 2. This initial analysis was not conducted on an intention to treat basis, however, a reanalysis on an intention to treat basis reported by the authors confirmed a significant 30% excess in standardized death rates from all causes in the clofibrate arm; Group 1 236/5331 versus Group 2 181/5296 P < 0.01 [627].

The cholecystectomy rate for gall stones was higher in group 1 (rate 2.1 per 1000 p.a, (P < 0.001) compared with groups 2 (rate 0.9 per 1000) and 3 (rate 0.9 per 1000) [1449].

This trial was one of the first large randomised controlled trials to be conducted and had some caveats. Olive oil capsules were given which are not considered a true placebo. The initial analysis was not conducted on a conventional intention to treat basis, however subsequent analysis on this basis was provided [627].

It should be noted that clofibrate has now been withdrawn from the British National Formulary.

The second randomised controlled trial [516] recruited asymptomatic men aged 40 to 55 years with dyslipidaemia (non-HDL cholesterol levels of ≥ 5.2 mmol/l on two successive measurements). A total of 4081 participants were randomised to receive either gemfibrozil or placebo and were followed up for five years. In addition, both groups were given advice to adopt a cholesterol-lowering diet, to increase physical activity and to reduce smoking and body weight.

Gemfibrozil therapy was associated with a 34% reduction (95% CI 8.2% to 52.6%) in the incidence of the combination outcome of fatal and nonfatal MI and cardiac death. After five years, the number of definite cardiac events in the gemfibrozil group was 56/2051 (an incidence rate of 27.3 per 1000) compared with 84/2030 in the placebo group (an incidence rate of 41.4 per 1000). There were no differences between groups in the total mortality rate.

Gemfibrozil therapy was associated with an increase in HDL cholesterol compared with baseline during the first year of more than 10%, this was followed by a small decline in HDL cholesterol with time. Gemfibrozil therapy was also associated with initial reductions in the levels of total cholesterol (11%), LDL cholesterol (10%), non-HDL cholesterol (14%) and triglycerides (43%). These changes were followed by a consistent level of total and LDL cholesterol and a small increase in triglyceride levels during the remaining time. Cholesterol levels did not differ significantly from baseline during the study in those allocated placebo [516].

During the first year, 11.3% of those randomised to receive gemfibrozil and 7% of those receiving placebo reported moderate to severe upper gastrointestinal symptoms (P < 0.001). During subsequent years, these rates decreased to 2.4% for the gemfibrozil group and 1.2% for the placebo group (P < 0.05). No significant difference between treatment groups were observed in the occurrence of constipation, diarrhoea, or nausea and vomiting [516].

Q.34.3 Cost effectiveness of fibrates

There were no cost effectiveness studies found on the use of fibrates compared with placebo in the prevention of CVD.

Q.34.4 Evidence to recommendations - fibrates

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.

Q.35 Nicotinic acids

Q.35.1 Evidence statements for nicotinic acids

No randomised controlled trials in people at high risk of CVD were identified that compared nicotinic acid therapy with placebo and reported cardiovascular event outcomes.

Q.35.2 Clinical effectiveness of nicotinic acids

No randomised controlled trials in people at high risk of CVD were identified that compared nicotinic acid therapy with placebo and reported cardiovascular event outcomes.

Q.35.3 Cost effectiveness of nicotinic acids

There were no cost effectiveness studies found on the use of nicotinic acids compared with placebo in the prevention of CVD.

Q.36 Anion exchange resins

Q.36.1 Evidence statements for anion exchange resins

One randomised controlled trial in men with elevated total and LDL cholesterol found that cholestyramine therapy was associated with a reduction in the incidence of the combination of CHD death and nonfatal MI but did not confer any benefit for the individual components of this outcome compared with placebo. Cholestyramine therapy was not associated with a reduction in all cause mortality compared with placebo.

Q.36.2 Clinical effectiveness of anion exchange resins

One randomised controlled trial, the Lipid Research Clinics Coronary Primary Prevention Trial was identified that compared anion exchange resin therapy with placebo in people at high risk of CVD [8,9].

This trial recruited men aged 35-59 years with a total cholesterol level of ≥ 6.88 mmol/l and an LDL cholesterol level of ≥ 4.92 mmol/l. A total of 3,806 men were randomised to receive either cholestyramine (24 g per day) or placebo. During a pre-randomisation phase, all participants received dietary advice which aimed to decrease total cholesterol levels by 3-5%. Participants were then followed up for a mean duration of 7.4 years [8,9].

Cholestyramine therapy was associated with a reduction in the primary endpoint of a combination of CHD death and nonfatal MI (reduction in risk 19%, 90% CI 3% to 32%, $P < 0.05$). Cholestyramine therapy did not confer any benefit compared with placebo for the individual components of this endpoint or for the outcome of all cause mortality.

Cholestyramine therapy was associated with a reduction in the secondary outcomes of development of angina ($P < 0.01$) and the development of a new positive exercise test result ($P < 0.001$) but did not confer any benefit compared with placebo for the outcomes of coronary bypass surgery or peripheral arterial disease.

Gastrointestinal side effects occurred more frequently in the group that received cholestyramine compared with those allocated placebo after 1 year (43% reported at least one gastrointestinal side effect in the placebo group versus 68% in the cholestyramine group). After seven years, incidence of side effects was similar between groups. There were no differences in the incidence of non gastrointestinal side effects between the groups [8,9].

Q.36.3 Cost effectiveness of anion exchange resins

There were no cost effectiveness studies found on the use of anion exchange resins compared with placebo in the prevention of CVD.

Q.36.4 Evidence to recommendations – anion exchange resins

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.

Q.37 Combination drug therapy

Q.37.1 Evidence statements for combination drug therapy

No randomised controlled trials with cardiovascular outcomes were identified that compared adding a fibrate, anion exchange resin, or nicotinic acid to a statin with statin monotherapy in people at high risk of CVD.

A systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports found the incidence of rhabdomyolysis to be ten fold higher when a statin was combined with the fibrate gemfibrozil.

Q.37.2 Evidence to recommendations – combination drug therapy

The GDG considered that there was insufficient evidence to recommend combining a statin with a fibrate, anion exchange resin, or nicotinic acid in primary prevention. In addition, it was noted that the combination of a statin with a fibrate may be associated with an increased risk of adverse events, in particular the combination of the fibrate gemfibrozil with a statin.

Q.38 Drug therapy for the secondary prevention of cardiovascular disease (CVD)

Q.38.1 Recommendations

54. When considering lipid modification therapy in primary and secondary prevention, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

Drug therapy for secondary prevention

55. For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comordbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- **smoking status**
- **alcohol consumption**
- **blood pressure (see 'Hypertension', NICE clinical guideline 34)**
- **body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)**
- **fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)**
- **fasting blood glucose**
- **renal function**
- **liver function (transaminases)**
- **thyroid-stimulating hormone (TSH) if dyslipidaemia is present.**

56. If a person has acute coronary syndrome, statin treatment should not be delayed until lipid levels are available. A fasting lipid sample should be taken about 3 months after the start of treatment.

Statins for secondary prevention

57. Statin therapy is recommended for adults with clinical evidence of CVD.

58. The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.

59. When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).20

60. People with acute coronary syndrome should be treated with a higher intensity statin. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.

61. Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

62. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity

statin21 should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

63. An 'audit' level of total cholesterol of 5 mmol/litre should be used to assess progress in populations or groups of people with CVD, in recognition that more than a half of patients will not achieve a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre.

Fibrates for secondary prevention

64. Fibrates may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Nicotinic acid for secondary prevention

65. Nicotinic acid may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Anion exchange resins for secondary prevention

66. Anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Monitoring of statin treatment for primary and secondary prevention

67. If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it.

68. People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured.

69. Creatine kinase should not be routinely monitored in asymptomatic people who are being treated with a statin.

70. Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

71. People who have liver enzymes (transaminases) that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.

72.If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought.

Q.39 Introduction to drug therapy for secondary prevention

Q.39.1 The effectiveness of lipid modifying drugs

The GDG based recommendations to use lipid modifying drugs on trial evidence of improvement in cardiovascular outcomes and where available, total mortality. For people with established CVD there is substantive trial evidence that statins reduce total mortality, cardiovascular mortality and morbidity and total mortality, and are cost-effective. This evidence is strongest for people with coronary heart disease (CHD).[131];[1007]

Among people with CHD treated with statins there is a reduction in recurrent CHD events of about 23%, (rate ratio (RR) 95% CI 0.74 to 0.80) and a reduction in stroke events by 17% (0.78 to 0.88).[131] For people with stroke there is a reduction in stroke and cardiovascular events using higher intensity statins.[84] No trials have compared the effectiveness of higher intensity statin therapy with standard intensity statin therapy in people following a stroke.

Although there have been no statin trials specifically in people with peripheral arterial disease (PAD), the Heart Protection Study demonstrated the benefits of statin therapy in patients with PAD. Allocation to simvastatin 40 mg daily reduced the rate of first major vascular events by about one-quarter, and that of peripheral arterial events by about one-sixth, with large absolute benefits seen in participants with PAD because of their high vascular risk.[630]

Fibrates have been shown to reduce some cardiovascular events in people with CHD though in comparison to statins their lower efficacy and adverse event profile has meant that statins are the drug of first choice for most people. Nicotinic acid and anion-exchange resins have also shown evidence of cardiovascular benefit.

The NICE Statin Technology Appraisal 'Statins for the prevention of cardiovascular events' 2006 has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost-effectiveness of statins, and our recommendations on the initiation of statin therapy are based upon this report which states that:

- Statin therapy is recommended for adults with clinical evidence of CVD
- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy
- When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

Q.39.2 The association between lipid modification using drugs and cardiovascular events

The epidemiological relationship between cholesterol as a risk factor in populations and groups and cardiovascular events is well established. As cholesterol increases, so does the risk of CVD. This relationship is such that each 1mmol/l rise in total cholesterol is associated with a 72% increase in the risk of a major coronary event.[464]

There is now compelling randomised controlled trial evidence in people with established CVD, that lowering cholesterol with statins reduces total mortality, cardiovascular mortality and morbidity. For the statin class at lower and moderate intensity each 1 mmol/l reduction in LDL cholesterol will

produce a proportional reduction in major vascular events of 23% (at least down to an LDL cholesterol of 2 mmol/l).[131]

Statins are highly cost-effective with a good record of safety. There is also good evidence that higher intensity statins are associated with additional cost-effective reductions in cardiovascular events for people after recent myocardial infarction (MI) and acute coronary syndrome (ACS).

However the benefits of cholesterol lowering and safety cannot be assumed for all drug classes or for all drugs within the same class[1114] and cardiovascular outcome and adverse event data should be available for every drug from clinical trials. The withdrawal of the statin cerivastatin because of adverse events is a salutary reminder that all drugs within a class are not the same and that there may be specific drug effects within a drug class.

The same strength of evidence that exists for statins does not exist for other classes of lipid lowering drugs (fibrates, anion exchange resins, nicotinic acid) where the trials are fewer in number, the total patient population studied can be small, and trials have shown variable benefits on cardiovascular events despite reduction in cholesterol.

Other classes of drug have either failed to improve cardiovascular outcomes or even increased mortality. Torcetrapib, one of a new class of lipid modifying drug therapies (CETP inhibitor) which raises HDL cholesterol, was being evaluated in a clinical trial which was stopped prematurely because of excess mortality.[711,1032]

The potential advantages of drug combinations from different classes cannot be assumed as there are no cardiovascular outcome data for any drug combination in lipid management. There is a greater propensity for major adverse events when statins are combined with fibrates or other drugs particularly when statins are used at higher doses.

Q.39.3 The use of statins in clinical practice

In the period 1981-2000, CHD mortality under age 84 years in England and Wales fell by 54%; 68 230 fewer deaths. Modelling of the effects of changes in the three major risk factors, smoking, blood pressure and serum cholesterol suggests that these changes are associated with 45 370 fewer deaths. The biggest single contribution to reduction in mortality was estimated to be a decrease in smoking. Approximately 2135 fewer deaths were attributed to statin treatment: 1990 in CHD patients and 145 in people without established disease.[1363]

Prescription of statins and other drugs to improve risk factors remains suboptimal despite the fact that half the survivors of hospital admission for acute MI or angina experience a further major coronary event or death within 5 years of discharge.[267]

Statin prescription has increased dramatically in the last 10 years particularly for people with established CVD. In 1997 Brady et al reported 18% of people with CHD in primary care were on statins.[209] In 2006, among 150 general practices in East London, statin prescription for people with CHD was 81% (Report: East London Clinical Effectiveness Group Queen Mary University of London 2007).

There is still considerable variation in prescribing and under-dosing by practice and evidence of inequity in prescribing by age and also by sex. Statins are less likely to be prescribed to people over 75 years and women.[407,429]

Patient adherence to treatment with statins remains a major challenge and only half the patients at highest risk after MI continue to take their statins at 2 years.[1078,1419]

Q.40 Statins

Q.40.1 Evidence statements for statins

NICE Technology Appraisal evidence statement for statins
In a meta-analysis of 14 randomised controlled trials of secondary prevention in CHD, statin therapy was associated with a reduction in all-cause mortality, CVD mortality, CHD mortality, fatal MI, and coronary revascularisation compared with placebo. [1007]

Q.40.2 Evidence statements for higher intensity statin therapy

Meta-analysis of four randomised controlled trials in patients with CHD found that higher intensity statin therapy compared with lower intensity statin therapy was associated with a reduction in the composite outcome of coronary death or MI, and with a reduction in the composite outcome of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or any revascularisation).
Higher intensity statin therapy was not associated with a reduction in all cause mortality but there was a trend for significance in cardiovascular mortality compared with lower intensity statin therapy. Higher intensity statins reduced coronary death or any cardiovascular event compared with lower intensity statins.
No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy in patients with peripheral arterial disease or following stroke.
One randomised controlled trial in patients following stroke or transient ischaemic attack found that higher intensity statin therapy with atorvastatin 80 mg was associated with a reduction in fatal stroke, the composite of fatal and non-fatal stroke and any cardiovascular event compared with placebo. Post-hoc analysis found this beneficial effect to be restricted to patients after ischaemic stroke whereas a harmful effect was found for those patients after haemorrhagic stroke.
Higher intensity statin therapy did not confer any benefit over placebo for the outcome of non-fatal stroke compared with placebo.
Using a model developed for the guideline, higher intensity statin therapy compared to low intensity statin therapy was found to be cost-effective in the base case in patients following acute coronary syndrome. Treatment is most cost-effective using drugs with lowest acquisition costs
Using a model developed for the guideline, higher intensity statin therapy is not cost-effective in the base case compared to low intensity statin therapy in patients with stable coronary artery disease (£27,840/QALY). However if generic drug prices are assumed high intensity statins will dominate lower intensity statins (they will result in more QALYs and cost savings) in patients with stable CAD.
Using a model developed for the guideline, a titration strategy based on a target total cholesterol of 4mmol/l was found to be cost-effective compared to a fixed dose strategy of low intensity statins, but only if titrating using generic drugs.
Adverse events associated with higher intensity statin therapy
Four randomised controlled trials in patients with CHD found that higher intensity statin therapy was associated with a greater persistent elevation in alanine aminotransferase and / or aspartate aminotransferase levels compared with lower intensity therapy. This was not found to be associated with a significant increase in clinical liver disease.
Three of the four trials found higher intensity statin therapy was not associated with an increase in myalgia compared with lower intensity therapy and one found an excess of myalgia but no increase in the incidence of myopathy.
Three of the four trials found that higher intensity statin therapy was not associated with an increase in rhabdomyolysis compared with lower intensity therapy and one found an excess of rhabdomyolysis in the higher intensity group which was found to be associated with identifiable secondary causes.
A retrospective analysis of pooled data from 49 clinical trials found higher intensity statin therapy with atorvastatin 80 mg to be associated with a greater incidence of persistent elevations in alanine aminotransferase and / or aspartate aminotransferase > 3 x ULN compared to standard intensity

therapy with atorvastatin 10 mg or placebo.
No incidences of myopathy or rhabdomyolysis were reported and serious hepatic adverse events were rare although a small number of patients receiving high intensity statin therapy developed hepatitis which resolved after discontinuation of drug therapy.

Q.40.3 Clinical effectiveness of statins

Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the 'line of no effect' i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal 94[1007] states that:

- Statin therapy is recommended for adults with clinical evidence of CVD.

The recommendation was based on the meta-analysis of 14 randomised controlled trials of secondary prevention in CHD. Of these, four were conducted in MI and / or angina patients (Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease.[16];[846];[1075];[1183] Four studies recruited patients with CAD[362,726,1094,1324] two studies recruited patients with CAD and hypercholesterolaemia[173,1158] one study recruited patients with mild CAD[1049] two studies enrolled patients after coronary balloon angioplasty[1229] and[172], and one study enrolled patients after percutaneous coronary intervention.[1228] Statin therapy was associated with a reduction in the following clinical outcomes compared with placebo: all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), unstable angina (RR 0.82, 95% CI 0.72 to 0.94), hospitalisation for unstable angina (RR 0.90, 95% CI 0.70 to 0.90), nonfatal stroke (RR 0.75, 95% CI 0.59 to 0.95), new or worse intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91) and coronary revascularisation (RR 0.77, 95% CI 0.69 to 0.85).

The NICE Technology Appraisal 94[1007] further states that:

- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy.
- When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

Q.40.4 Clinical effectiveness of higher intensity versus lower intensity statin therapy

No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in patients with angina alone, stroke or peripheral arterial disease. In addition, no randomised controlled trials were identified on the effectiveness of up-titrating statin dose compared with giving a fixed dose.

Three randomised controlled trials compared higher intensity statin therapy with lower intensity statin therapy in patients with CHD: one in patients after ACS (PROVE-IT-TIMI-22)[265], one in patients with previous MI (IDEAL) [1074] and one which included previous MI 58% and/or angina/revascularization (TNT).[811] None of these trials treated to a pre-specified target total or LDL cholesterol, although the achieved levels were lower in each of the higher intensity statin groups,

compared with the respective lower intensity statin groups. A fourth trial in patients after ACS, compared early intensive statin therapy with delayed conservative statin therapy (A to Z).[398]

The first randomised controlled trial[265] recruited patients within 10 days of an ACS event (29% had unstable angina, 36% non-ST elevation MI and 35% ST elevation MI). A high proportion of trial participants were taking other secondary prevention drugs and over two thirds were revascularised for treatment of the index event. At recruitment patients had to have a total cholesterol of 6.21 mmol/l or less. Patients were randomised to receive either higher intensity statin therapy with atorvastatin (80 mg once daily) or lower intensity statin therapy with pravastatin (40 mg once daily). Lipid values at the start of the study were similar in both groups. At follow up, patients in the atorvastatin group achieved lower levels of LDL cholesterol compared with the pravastatin group (1.60 mmol/l versus 2.46 mmol/l) and patients in the pravastatin group achieved higher HDL cholesterol levels.

During a mean follow up of 24 months, there was a reduction in the primary outcome (a composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation or stroke) with higher intensity therapy compared with lower intensity (HR 0.84, 95% CI 0.74 to 0.95). Similarly, higher intensity therapy was associated with a risk reduction of 14% (P = 0.029) for the secondary outcome of a composite of death from CHD, nonfatal MI or revascularisation. There was no significant reduction in death from any cause or reinfarction with higher intensity therapy compared with lower intensity.[265]

The second study was an open label randomised trial in patients with prior MI (median time since last MI was 22 months).[1074] Most trial participants were taking aspirin and beta blockers, but almost 2/3 were not taking ACE inhibitors or ARBs. Patients were assigned to higher intensity atorvastatin 80 mg once daily or lower intensity simvastatin (20 mg once daily). Further drug titration could be undertaken at 24 weeks within the study protocol, based on achieved total cholesterol levels. Twenty one percent of patients in the simvastatin group had their dose increased to 40 mg daily, and 6% of patients in the atorvastatin group had their dose reduced to 40 mg daily. At the end of the study, 23% were treated with simvastatin 40 mg daily and 13% with atorvastatin 40 mg daily. During treatment, patients in the atorvastatin group had lower levels of LDL cholesterol, total cholesterol, triglycerides and apolipoprotein B compared with the simvastatin group. HDL cholesterol and apolipoprotein A1 levels were higher in the simvastatin group compared with the atorvastatin group. Mean LDL cholesterol levels were 2.7 mmol/l in the simvastatin group and 2.1 mmol/l in the atorvastatin group.

For the primary endpoint of major coronary event (defined as coronary death, hospitalisation for nonfatal acute MI, or cardiac arrest with resuscitation) there was no significant difference in event rates between the two treatment groups during a median follow up of 4.8 years. There was a reduction in the nonfatal MI component of this primary endpoint with atorvastatin therapy compared with simvastatin treatment (HR 0.83, 95% CI 0.71 to 0.98). Atorvastatin treatment was associated with a reduction in the secondary endpoint of any CHD event (HR 0.84, 95% CI 0.76 to 0.91) and also a reduction in any major cardiovascular event (HR 0.87, 95% CI 0.78 to 0.98) compared with simvastatin treatment. There were no differences in cardiovascular or all cause mortality.[1074]

The third randomised controlled trial recruited patients with clinically evident stable CHD (59% had a prior MI, 82% angina).[811] To ensure that, at baseline, all patients had LDL cholesterol levels consistent with the then current guidelines for the treatment of stable CHD, patients with LDL cholesterol levels between 3.4 and 6.5 mmol/l entered an eight week run in period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run in phase, those patients with a mean LDL cholesterol of less than 3.4 mmmo/l were randomised. Patients were assigned to either higher intensity atorvastatin (80 mg once daily) or lower intensity atorvastatin (10 mg once daily). The trial follow up was for a median of 4.9 years. No information was given on concomitant medications at baseline or during the trial but it was stated that medication usage was similar in the two groups at the start of

the trial. Mean LDL cholesterol levels during the study were 2.0 mmol/l in the group treated with atorvastatin 80 mg once daily and 2.6 mmol/l in the group treated with atorvastatin 10 mg once daily. There was a 22% reduction (95% CI 11% to 31%) in the primary end point (defined as the combination of death from CHD, nonfatal non-procedural MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) in patients treated with atorvastatin 80 mg daily compared with patients treated with atorvastatin10 mg daily. Patients treated with high dose atorvastatin had a decreased incidence of the following components of this primary endpoint: nonfatal MI (HR 0.78, 95% CI 0.66 to 0.93), and fatal or nonfatal stroke (HR 0.75, 95% CI 0.59 to 0.96). Higher intensity treatment was also associated with a lower incidence of the following secondary outcomes: major coronary event (HR 0.80, 95% CI 0.69 to 0.92), cerebrovascular event (HR 0.77, 95% CI 0.64 to 0.93), hospitalisation for congestive heart failure (HR 0.75, 95% CI 0.59 to 0.93), any cardiovascular event (HR 0.81, 95% CI 0.75 to 0.87) and any coronary event (HR 0.79, 95% CI 0.73 to 0.86). There was no difference in all cause mortality between higher and lower intensity atorvastatin treatment.[811]

A fourth trial compared early intensive statin therapy with delayed lower intensity statin therapy (A to Z).[398] This trial consisted of 2 overlapping phases. The first phase was an open labelled trial comparing enoxaprin with unfractionated heparin in patients with non ST elevation ACS who were treated with tirofiban and aspirin. The second phase recruited patients initially from the first phase who had stabilised (for at least 12 consecutive hours within 5 days after symptom onset). In addition, recruits had at least one of the following characteristics: age older than 70 years, diabetes mellitus, prior history of coronary artery disease, peripheral arterial disease or stroke. Subsequently, the protocol was amended to allow patients with non ST elevation ACS who were not enrolled in the first phase, and also patients with ST elevation MI to enter into the second phase directly (overall non ST-segment elevation ACS: 60%, ST elevation MI: 40%).

At baseline almost all the participants were taking aspirin and beta blockers, three quarters were taking ACE inhibitors and almost half were revascularised for treatment of the index event. Patients were randomised to either simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter (early higher intensive therapy) or placebo for 4 months followed by simvastatin 20 mg once daily thereafter (delayed conservative therapy).[398]

Early high intensity statin therapy decreased LDL cholesterol levels by 39% compared with baseline levels during the first month of therapy with simvastatin 40 mg, and then by a further 6% following an increase in simvastatin dosage to 80 mg. For the delayed conservative statin treatment group, LDL cholesterol levels increased by 11% during the 4 month placebo period, then decreased from baseline by 31% after 4 months of therapy with simvastatin 20 mg.[398]

For the primary endpoint of the combination of cardiovascular death, nonfatal MI, readmission for ACS or stroke, early higher intensity statin therapy did not confer benefit compared with delayed lower intensity therapy. There was also no benefit found in any of the individual components of the primary endpoint. Likewise no benefit was observed in the secondary endpoints of all cause mortality and coronary revascularisation due to documented ischaemia. There was a reduction in the incidence of new onset congestive heart failure in the early intensive statin treatment group compared with the delayed conservative treatment group (HR 0.72, 95% CI 0.53 to 0.98) but not a reduction in cardiovascular related death (HR 0.75, 95% CI 0.51 to 1.00).[398]

A meta-analysis of these four studies has been conducted by Cannon et al[266] using a fixed-effects model. Higher intensity statin therapy did not confer any significant benefit over lower intensity statin therapy for the outcomes of all cause mortality (OR 0.94, 95 % CI 0.85 to 1.04), cardiovascular mortality (OR 0.88, 95 % CI 0.78 to 1.00) or non-cardiovascular mortality (OR 1.03, 95 % CI 0.88 to 1.20). Higher intensity statin therapy was associated with a reduction in the combination of coronary death or MI (OR 0.84, 95 % CI 0.77 to 0.91), stroke (OR 0.82, 95 % CI 0.71 to 0.96) and coronary death or any cardiovascular event (OR 0.84, 95 % CI 0.80 to 0.89).

In addition to the four trials comparing higher intensity therapy with lower intensity therapy, two randomised controlled trials were identified that compared higher intensity statin therapy with placebo. The first trial recruited patients with ACS[1219] and the second recruited patients with a history of stroke or transient ischaemic attack.[83]

The trial in patients with ACS[1219] randomised a total of 3086 patients with unstable angina or non-Q-wave acute MI to receive either atorvastatin 80 mg daily or placebo. Patients were hospitalised within 24 hours of the index event and randomised after a mean of 63 hours of hospitalisation. During or after hospitalisation for the index event, most were treated with aspirin, three quarters with beta blockers and half with ACE inhibitors or ARBs.

The study period was for 16 weeks and during this period the primary end point (combination of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalisation) was not significantly reduced in patients randomised to atorvastatin compared with those who received placebo (RR 0.84, 95% CI 0.70 to 1.00). Atorvastatin therapy was not associated with a reduction in the following individual components of the primary outcome: death, non-fatal MI or cardiac arrest with resuscitation but was associated with a lower risk of recurrent myocardial ischaemia requiring rehospitalisation compared with placebo (RR 0.74, 95% CI 0.57 to 0.95). However, it should be noted that the study was only powered to detect differences between groups in the primary outcome. At the end of the study, compared to baseline, LDL cholesterol had increased by an adjusted mean of 12% in the placebo group and had decreased by an adjusted mean of 40% in the atorvastatin group.[1219]

Incidences of the following secondary outcomes were not different in the atorvastatin group compared with placebo: coronary revascularisation procedures, worsening congestive heart failure or worsening angina. Non-fatal stroke was reduced in the atorvastatin group compared with placebo (RR 0.41, 95% CI 0.20 to 0.87) as was the composite outcome of fatal and non-fatal stroke (RR 0.50, 95% CI 0.26 to 0.99).[1219]

The second randomised controlled trial[83] recruited patients without known CHD and with previously documented stroke (69%) (66.5% ischaemic and 2.5% haemorrhagic) or transient ischaemic attack (31%), 1 to 6 months prior to randomisation. A total of 4731 participants were randomised to receive either 80 mg atorvastatin or placebo and were followed up for a mean duration of 4.9 years. Most patients were taking aspirin or other antiplatelets (not heparin) although only 29% were taking ACE inhibitors and 18% beta blockers. For the primary endpoints, high dose atorvastatin decreased the risk of fatal stroke (HR 0.57, 95 % CI 0.35 to 0.95) and the composite of fatal and non-fatal stroke (HR 0.84, 95 % CI 0.71 to 0.99) compared with placebo. High dose atorvastatin also reduced the risk of any cardiovascular event (stroke plus any major coronary event) (HR 0.80, 95 % CI 0.69 to 0.92) compared with placebo. No benefit was found for the outcome of non-fatal stroke. Post hoc analysis indicated significant differences in hazard ratios based on the type of stroke occurring during the trial; the cause specific adjusted hazard ratios compared to placebo showed a beneficial effect in those experiencing ischaemic stroke during the trial (HR 0.78, 95 % CI 0.66 to 0.94), but a harmful effect on those experiencing haemorrhagic stroke (HR 1.66, 95 % CI 1.08 to 2.55). Atorvastatin conferred benefit compared with placebo for the following secondary outcomes: major coronary event (HR 0.65, 95 % CI 0.49 to 0.87), major cardiovascular event (HR 0.80, 95 % CI 0.69 to 0.92), any cardiovascular event (HR 0.74, 95 % CI 0.66 to 0.83), acute coronary event (HR 0.65, 95 % CI 0.50 to 0.84), any coronary event (HR 0.58, 95 % CI 0.46 to 0.73), non-fatal MI (HR 0.51, 95 % CI 0.35 to 0.74), revascularisation (HR 0.55, 95 % CI 0.43 to 0.72), transient ischaemic attack (HR 0.74, 95 % CI 0.60 to 0.91), the composite of stroke or transient ischaemic attack (HR 0.77, 95 % CI 0.67 to 0.88). No benefit was seen for the outcomes of cardiovascular mortality or all cause mortality but the trial was not statistically powered for this endpoint.[83]

Q.40.5 Cost-effectiveness of statins

The NICE Technology Appraisal[1007] states that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Q.40.6 Cost-effectiveness of higher intensity statin therapy compared with lower intensity statin therapy

When initial searches were undertaken, no studies were found which compared cost-effectiveness of higher intensity statins with lower intensity statins in patients with coronary artery disease (CAD). Consequently, the GDG requested the development of an economic model to help inform the guideline.

A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins (atorvastatin 80 mg and simvastatin 80 mg) compared with low intensity statins (simvastatin 40 mg) from a UK NHS perspective. The base case assumptions model two cohorts of hypothetical patients aged 65 years of age:

(b) Patients with acute ACS, and;

(c) Patients with stable coronary artery disease (CAD).

Intermediate outcomes included in the model include the numbers of MI, stroke, TIA, PAD, heart failure, revascularisation, and angina events, and deaths from CVD and other causes. Effectiveness data for ACS patients were drawn from two studies which were meta-analysed; A to Z[398], in which patients were randomised to either simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter (early intensive therapy) or placebo for 4 months followed by simvastatin 20 mg once daily thereafter (delayed conservative therapy) and PROVE-IT where patients were randomised to receive either higher intensity statin therapy with atorvastatin (80 mg once daily) or lower intensity statin therapy with pravastatin (40 mg once daily).[265] For the stable CAD patient model, effectiveness data were drawn from the TNT where patients were assigned to either higher intensity atorvastatin (80 mg once daily) or lower intensity atorvastatin (10 mg once daily)[811] and IDEAL where patients were assigned to higher intensity atorvastatin 80 mg once daily or lower intensity simvastatin (20 mg once daily)[1074] trials. Again, these were meta-analysed.

The models make the conservative assumption that the all cause mortality rate in the modelled population is twice that of the general population. Health state utility values were taken from published sources (see Appendix C for details). All cause mortality rates were taken from the Government Actuarial Department.[578] The model makes the conservative assumption of no adverse events from treatment using high intensity statins. Cost of drugs were taken from the Prescription Pricing Authority Drug Tariff Feb 27th 2008 (atorvastatin 80 mg £367.74/year, simvastatin 80 mg £64.53/year, simvastatin 40 mg, £18.12/year).[1022] Costs of cardiovascular events were taken from the statins TA94.[1007] In order to reflect social values for time preference, as is standard in economic models, costs and QALYs have been discounted at 3.5% as recommended by NICE[1007] All of these and other model assumptions have been tested in sensitivity analyses.

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY.

Q.40.7 Results for patients with ACS

Table 2 indicates the modelled number of events for a hypothetical population of 1,000 ACS patients treated with either high intensity or low intensity statins. The table indicates that fewer

cardiovascular events occur in the population treated with high intensity statins. This translates to a gain of 0.32 discounted QALYs when compared with low intensity statins.

Table 2 Lifetime modelled events for a cohort of 1,000 ACS patients treated with either low or high intensity statins

Health state	Low Intensity	High Intensity
MI	386	400
Stroke	112	102
Heart Failure	317	246
Revascularisations	444	431
Unstable Angina	270	258
Cardiovascular Mortality	389	333
Death from other causes	611	667

a) Cost-effectiveness results for ACS patients

The model estimates the life-time incremental cost per QALY of using high intensity statins (both simvastatin and atorvastatin 80mg) compared with low intensity statins both simvastatin and pravastatin is about £4,700, indicating that high intensity statins are cost-effective in ACS patients. The probability that high intensity statins is cost-effective is about 94% when compared with low intensity statins.

Q.40.8 Results for patients with stable coronary artery disease (CAD)

Table 2 indicates the modelled number of lifetime events for a hypothetical 1000 patients treated with either high or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated high intensity statins. This translates to a gain of 0.08 discounted QALYs per patient when compared with low intensity statins.

Table 3: Lifetime modelled events for a cohort of 1000 CAD patients treated with either low or high intensity statins

Health state	Low Intensity	High Intensity
MI	170	138
Stroke	134	102
Transient Ischemic Attack	60	51
Peripheral Artery Disease	63	59

Heart Failure	109	81
Revascularisations	224	181
Unstable Angina	126	103
Cardiovascular Mortality	424	416
Death from other causes	576	584

- Cost-effectiveness results

The model estimates the life-time incremental cost per QALY of using high intensity statins (atorvastatin 80mg) compared with low intensity statins (simvastatin 40mg) is about £27,840 indicating that high intensity statins are not cost-effective in patients with stable CAD. The probability that high intensity statins is cost-effective is about 42% when compared with low intensity statins.

Updated Economic Publication Searches

Subsequent to this model being built, updated searches retrieved one publication which compared higher intensity statins with lower intensity statins in patients with ACS and stable CAD in North America.[294] The study is a cost-utility analysis conducted from a third payer's perspective, using a Markov model for a hypothetical population of 60 year old patients. Effectiveness data were drawn from the A to Z[398] and PROVE-IT [265] trials for the ACS model, and from the TNT [811] and IDEAL [1074] trials for the stable CAD model. Utility data were derived from published literature. The estimated ICER for the ACS population was below US$30,000/QALY and is stable in sensitivity analysis. The ICER for the stable CAD population was reported as US$33,400/QALY but the ICER is very sensitive to assumptions about statin efficacy (ICER range from $10,300/QALY to dominated) and cost of statins. ICERs range from dominant using the lower price of atorvastatin to $84,000/QALY when the higher price is used. The results of this study are similar to those found as a result of our modelling work.

Summary of cost-effectiveness of higher versus lower intensity statins

In conclusion, compared with low intensity statins, high intensity statins in patients with ACS are cost-effective when compared with low intensity statins. In patients with stable CAD, atorvastatin 80 mg is not cost-effective using a £20,000/QALY threshold. However, assuming the use of generic simvastatin 80 mg is makes the model highly cost-effective. Thus cheaper generic high intensity statins may be used in patients with stable CAD.

Cost-effectiveness of treating to target (titration threshold) compared with fixed doses of statins

A systematic literature search identified 408 papers. Eighteen papers were assessed in full. None of them met the inclusion criteria. In light of the lack of published evidence, the GDG requested the development of an economic model in order to generate cost-effectiveness estimates.

Model Structure and Assumptions

The population modelled is a hypothetical cohort of 1000 adults with hyperlypidemia and with a history of CHD/CVD, and who are free from diabetes. The population modelled was based on a distribution of patients taken from The Health Improvement Network (THIN) database, having an average untreated total cholesterol level of 6.1 mmol/l and an average age of 61 years.

The model estimates lifetime costs and quality adjusted life years (QALYs) of statin treatment using a target titration treatment strategy versus a fixed dose treatment strategy. The model has been used to estimate the cost-effectiveness of both 4 mmol/l and 5 mmol/l targets using 1 and 2 step titrations.

In the fixed dose strategy, all patients are assumed to be given simvastatin 40 mg daily, with no further consultations, or measurements performed. This treatment strategy was initially compared with a two-stage titration strategy, in which patients are initially given simvastatin 40 mg daily, with those failing to reach the pre-specified target then being titrated to the next therapy (simvastatin 80 mg). Measurements are again taken for the latter group of patients, and anyone still not achieving the pre-specified target is then assumed to be titrated up to atorvastatin 80 mg. In the one-step titration model, patients not achieving target on simvastatin 40 mg are titrated once only up to simvastatin 80 mg, with no further up-titration.

For both treatment arms, the modelled percentage reductions in cholesterol levels are estimated using the results of the STELLAR trial.[720] Subsequent reductions in CVD event and mortality outcomes were estimated using equations derived from a meta-analysis by Law et al.[819]

Costs of drugs are based on prices quoted by the PPA as at February 27th 2008.

Table 4: Costs of modelled Statins as at Feb 27th 2008

	Price per 28 pack	Annual Cost
Simvastatin 40 mg	£1.39	£18.12
Simvastatin 80 mg	£4.95	£64.53
Atorvastatin 80 mg	£28.21	£367.74

Each titration step is assumed to cost £26 based on the cost of a GP consultation and a blood test.[1015] Cost of health states including treatment for MI, stroke, TIA, PAD, HF, and angina were estimated using various published sources (details in Appendix C). Health state utility values were taken from published sources (Appendix C). All cause mortality rates are from the Government Actuarial Department.[578] The model makes the conservative assumption that the all cause mortality rate in the modelled population is twice that of the general population. Also, the model assumes no adverse events from treatment using high dose statins.

As recommended by NICE[1007] and to reflect social values, future costs and QALYs are both discounted at a rate of 3.5% in the model. These and other model assumptions have been tested in sensitivity analyses.

Results

Table 5 indicates that with a target of 5 mmol/l total cholesterol, the majority of patients (69%) are modelled to reach target on simvastatin 40 mg. This is true of both the fixed and the titration population groups in the model. With a target of 4 mmol/l, only 31% of patients will reach target on simvastatin 40 mg. In the 2 step titration model an additional 15% of patients reach target on simvastatin 80 mg, if the target is 5 mmol/l and an additional 6% reach target using 4 mmol/l.

Table 5: Proportion of patients modelled to be on each of the three included drugs under four treatment strategies

	2-Step Target 5	2-Step Target 4	1-Step Target 5	1-Step Target 4

Simva 40 mg	69%	31%	69%	31%
Simva 80 mg	15%	6%	31%	69%
Atorva 80 mg	16%	63%	-	-

Table 6 indicates the modelled number of events for the hypothetical 1000 patient cohorts having assumed a 2-step titration and a target total cholesterol of 5 mmol/l for illustrative purposes. The table indicates that fewer CVD events occur in the population treated using the titration strategy.

Table 6: Lifetime event outputs modelled for a cohort of 1,000 patients using a 2-stage titration treatment strategy with a target of 5 mmol/l total cholesterol compared with a fixed low dose treatment strategy

	F&F	**Titration to 5 mmol/l**			
	sim 40	**sim 40**	**sim80**	**Atorva80**	**Titration Total**
No of patients	1000	690	150	160	1000
Total MIs	135	93	18	16	127
Total Strokes	168	116	25	26	167
total TIA	86	59	13	14	86
Total PAD	60	41	8	8	57
Total HF	78	54	11	9	74
Total Stable Angina	184	127	25	22	174
Total Unstable Angina	94	65	13	12	90
CVD deaths	104	72	14	13	99
Other Deaths	896	618	136	147	901
Titration costs	-				£34,060
Tot. Discounted Costs	£9,280,374				£10,002,892
Discounted QALYS	8,116				8135

The incremental cost-effectiveness analysis indicates that compared to a fixed dose treatment strategy, a 1-step titration to simvastatin 80mg treatment strategy using a target of 4mmol/l has an ICER of £14,089 per QALY. One step titration to 5mmol/l is ruled out by extended dominance and 2 – step titration to 5 is dominated by I step titration to 4mmol/l. Two step-titration to 4mmol/l is not cost-effective and has an ICER of £66,819/QALY when compared to 1 step-titration to 4mmol/l. Our model indicates that with the 1 step titration to a target of 4 mmol/l (simvastatin 80mg) 63% of patients would not achieve this target, however the analysis indicates that it would not be cost-effective to try to get more patients to target.

Conclusion

In conclusion, the result of modelling suggest that titration using a threshold target of 4 mmol/l total cholesterol is cost-effective so long as titration stops at simvastatin 80 mg. Most patients would not achieve a target of 4mmol/l total cholesterol and modelling suggests that it is not cost-effective to try to take more patients to target using higher cost statins such as atorvastatin. Details of the economic model and the analyses are available in Appendix C.

Q.40.9 Adverse events associated with lower intensity statin therapy

Adverse events associated with lower intensity statin therapy are discussed in the primary prevention drug therapy chapter (Section 6.3.2.3).

Q.40.10 Adverse events associated with higher intensity statin therapy

Four randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy, the details and results of which have been described in section 1.3.3.[265,398,811,1074]

The first trial[265] found elevations in alanine aminotransferase levels to be greater in patients who received atorvastatin 80 mg compared with those receiving pravastatin 40 mg. Discontinuation of study medication due to myalgia, muscle aches or elevations in creatine kinase levels were similar in the two treatment groups. No cases of rhabdomyolysis were reported in either group.[265]

The second trial[1074] found that patients who received atorvastatin 80 mg had higher rates of discontinuation due to non-serious adverse events than those allocated to simvastatin 20 mg. There were no differences in the frequency of serious adverse events between the two treatment groups. Serious myopathy and rhabdomyolysis were rare in both groups [1074].

The third trial[811] found therapy with atorvastatin 80 mg to be associated with an increase in adverse events, with a higher rate of treatment discontinuation compared with the atorvastatin 10 mg group. Treatment related myalgia was similar in the two groups and there were no persistent elevations in creatine kinase. Five cases of rhabdomyolysis were reported (2 in the high dose group, 3 in the low dose group). More patients in the high dose group had persistent elevation in alanine aminotransferase, aspartate aminotransferase or both, compared with the low dose group.[811]

The fourth trial[398] compared early intensive therapy (simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter) with delayed conservative therapy (placebo for 4 months followed by simvastatin 20 mg once daily thereafter). Incidences of elevated alanine aminotransferase or aspartate transaminase levels (greater than 3 X ULN) were found to be similar in the two treatment groups. Discontinuation of study medication due to muscle-related adverse events was also comparable between the two groups. A total of 10 patients developed myopathy (creatine kinase > 10 X ULN on 2 consecutive measurements). Of the nine patients treated with simvastatin 80 mg, three patients had creatine kinase levels > 10 000 units/l and met the criteria for rhabdomyolosis. Of these 3 patients, 1 had contrast media renal failure and 1 patient was receiving concomitant verapamil (inhibitor of cytochrome P450 3A4 (CYP3A4)). In addition, 1 patient receiving 80 mg simvastatin had a creatine kinase level 10 X ULN without muscle symptoms, which was associated with alcohol abuse.[398]

Two randomised controlled trials were identified that compared higher intensity statin therapy with placebo[83,1219], the details and results of which have also been described in section 9.3.3.

The first trial[1219] found that more patients in the atorvastatin 80 mg group developed liver transaminase levels > 3 X ULN compared with those allocated placebo. There were no cases of myositis.

The second trial[83] compared treatment with atorvastatin 80 mg to placebo and found no significant difference in the incidence of serious adverse events between groups, although persistent elevation of alanine or aspartate aminotransferase (> 3 ULN on two consecutive occasions) was more frequent in the atorvastatin group (2.2 %) versus placebo (0.5 %), P < 0.001.

A retrospective analysis of pooled data from 49 clinical trials of atorvastatin was identified which compared the relative safety of lower intensity atorvastatin 10 mg with higher intensity atorvastatin 80 mg.[1020] Data were pooled from 49 clinical trials (n = 14 236 participants) in which patients were randomised to receive active treatment for a period ranging from 2 weeks to 52 months (atorvastatin 10 mg: n = 7258, atorvastatin 80 mg: n = 4798 and placebo: n = 2180). The incidence rate (per 1000 patient-years of exposure) of various safety parameters and adverse events was calculated for each of the three groups. The overall safety profile was comparable between atorvastatin 80 mg, 10 mg and placebo in terms of incidence rate of patients experiencing ≥1 adverse event, withdrawals due to adverse events and serious, nonfatal adverse events. Musculoskeletal safety parameters were also similar across groups and there were no incidences of myopathy or rhabdomyolysis reported. In this analysis, a greater incidence of persistent alanine aminotransferase and / or aspartate aminotransferase > 3 X ULN was observed in the atorvastatin 80 mg group compared with the other two groups. Serious hepatic adverse events were rare although five patients in the atorvastatin 80 mg group developed hepatitis, which resolved after discontinuation of atorvastatin. The adverse events of haematuria and albuminuria were also examined but the incidence in each atorvastatin group was low compared to placebo. Incidence of death was low in all groups and none were considered to be related to treatment.

A number of cohort studies have examined the safety of rosuvastatin used in clinical practice.

The first was a Dutch study that followed three separate cohorts, namely incident rosuvastatin users, other incident cohort users and non-statin exposed controls for cases of myopathy, rhabdomyolysis, acute renal failure and liver impairment / failure.[561] Exclusion criteria for the two statin cohorts were as follows; not incident users, statin use < 12 months, age < 20 or > 84 years, missing information in the PHARMO system, serious adverse event in history (e.g. of myopathy, rhabdomyolysis). The control cohort had to be aged between 20 and 84 and have no history of statin usage (≥ 12 months), and individuals were excluded if they had a history of a serious adverse event (e.g. of myopathy, rhabdomyolysis). Data were obtained from the PHARMO medical record linkage system that included drug-dispensing records from community pharmacies and hospital discharge records of more than 2 million residents throughout the Netherlands. Potential cases of hospitalisation for myopathy, rhabdomyolysis, acute renal failure or hepatic impairment for each of the three cohorts were validated through a multi-step process using data obtained from hospital records. Cases of all cause mortality were obtained from notifications in the hospital and pharmacy databases and were not validated.[561]

In 2002 and 2004, of 119 681 statin users 47 543 incident statin users met the inclusion criteria. More than 20% of those patients started with rosuvastatin (10 147), 15 091 patients with atorvastatin, 14 198 with simvastatin, 7290 with pravastatin and 817 with floatation. There were 99 935 controls selected from the PHARMO system. In total, 102 events (excluding death) were identified in 96 patients, 21 in the category myopathy/rhabdomyolysis, 48 in acute renal failure, and 33 events as hepatic Impairment. Only 81% of cases could be validated (79.4%) because some hospitals did not cooperate for several not medical reasons. The validation process resulted in 1 case of myopathy, 1 case of rhabdomyolysis, 13 cases of renal impairment and 11 cases of hepatic impairment. The total number of deaths identified was 1388, and after adjustment for age and gender in the three cohorts, all cause mortality was not increased in the statin user groups compared with the control group.[561]

The total incidence of serious adverse event was very low, in the users of statins only 15 validated events were identified in more than 45 000 years of follow up (> 1 per 3000 person years). Only one

case of myopathy could be identified among the users of other statins cohort, and one case of rhabdomyolysis in the non statin control cohort. The number of validated cases of acute renal failure was higher, and the incidence in both statin cohorts was increased compared with controls (rosuvastatin RR 5.91, 95%CI 1.19 to 29.36, other statins RR 3.27 95%CI 0.84 to 12.75). No significant difference was observed in the incidence of acute renal failure between the rosuvastatin and other statin cohorts (RR 1.81, 95%CI 0.47 to 7.02). Hepatic impairment incidences' were comparable in the other statin and control cohorts, while no incidences of hepatic impairment were found in the rosuvastatin cohort[561]

The second study was an observational cohort study in which patients were identified from dispensed prescriptions issued by primary care physicians / general practitioners between August and December in the England.[740] At least 6 months after the initial prescription, questionnaires known as Green forms were sent to the general practitioners requesting information regarding any event that occurred since initiation of rosuvastatin. The term event was defined as 'any new diagnosis, any reason for referral to a consultant or hospital admission, any unexpected deterioration (or improvement in concurrent illness, and suspected drug reaction, any alteration of clinical importance in laboratory values, or any other significant event requiring documentation. All returned forms were reviewed by medically qualified staff, and events that required further assessment were followed up. These included muscular, hepatic and renal events, suspected adverse drug events, and events with unknown aetiology for example jaundice.[740]

Of 31 228 Green forms sent, 12 543 (40.2%) were returned, and 863 (6.9%) were classified as void and excluded from the study. The study cohort comprised of 11 680 patients, of which 50.3% were male (5880), 49.2% (5745) were female, and for 0.5% (55) the sex was not specified. The median age was 64 years (interquartile range 56 to 72 years), and the age range was 17 to 101 years. The median treatment period was 9.8 months (interquartile range 4.6 to 11.7 months).[740]

Data derived from the Green forms were used in an incident density analysis of all events reported during treatment within specified time periods and also provided information on clinical events reported as the reason for discontinuation of rosuvastatin.[740]

A total of 2047 (17.5%) patients were reported to have stopped treatment with rosuvastatin. Musculoskeletal events accounted for 20.3% (414 of 2037) of the reasons for discontinuation. Myalgia was the most frequents cause (277 cases, 13.6% of all reasons specified), followed by patient request (144 of 2037), drug information including adverse publicity / reports in the media (123 of 2037), non formulary reasons such as change in general practitioner, prescribing policy (91 of 2037). Abnormal liver function tests and elevated creatine kinase levels accounted for 57 and 33 cases of discontinuation, respectively.[740]

Incident densities (ID) were calculated for events occurring in the first month (ID1) of treatment, during months 2-6 (ID2-6) of treatment and for events occurring during the overall treatment period. The ten most common adverse events in order of first month IDs were: Myalgia, malaise, dizziness, nausea/vomiting, intolerance, headache / migraine, abdominal pain, dyspepsia, abnormal LFTs and joint pain. Myalgia was the adverse event with the highest incident density during month 1 (ID1 = 7.70 events per 1000 patient-months of treatment) and it also had the highest ID for the whole treatment period. The difference between IDs for the first month and during months 2-6 were calculated to establish which events may have been early-onset events with rosuvastatin. There were six clinical events for which the rate of event in month 1 was significantly greater than the rate of event in months 2-6: Myalgia (ID1-ID2-6 = 4.0 (99% CI 1.67 to 6.33)), malaise (ID1-ID2-6 = 2.28 (99% CI 0.64 to 3.91)), dizziness (ID1-ID2-6 = 1.90 (99% CI 0.49 to 3.30)), nausea / vomiting (ID1-ID2-6 = 1.54 (99% CI 0.17 to 2.91)), intolerance (ID1-ID2-6 = 1.71 (99% CI 0.38 to 3.04)), and headache / migraine (ID1-ID2-6 = 1.43 (99% CI 0.11 to 2.75)).[740]

IDs were also stratified by starting dose of rosuvastatin: the IDs for the 20 mg/day and 40 mg/day dosages were compared with the 10 mg/day dose. A 2.5 fold increase in the rate of abnormal LFT

results was found for patients started on the rosuvastatin 40 mg/day dose compared with those started on the 10 mg/day dose (Incidence density ratio = 2.71 (95% CI 1.53 to 4.53)). Although there was an increase in the incidence density ratio for the 40 mg/day dose compared with the 10 mg/day dose for elevated CK, raised urea / creatinine, haematuria and proteinuria, these differences were not significant. No differences were found between dosage groups in the rates of myalgia, limb pain or cramps.[740]

Where events described on the Green forms required further assessment, follow-up questionnaires were sent to the GPs. A total of 685 questionnaires were posted to prescribing GPs of which 585 (85%) were returned. Data from these questionnaires were used in a causality assessment for adverse events relating to the muscular, hepatic and renal system-organ classes. Events were assessed as 'probably' or 'possibly' related to rosuvastatin depending upon various factors including whether the adverse events were clinically and/or pathologically well-defined with reasonable time-sequence in relation to administration of rosuvastatin and whether they were more likely to be attributed to rosuvastatin than to concurrent disease or other drugs and whether dechallenge or rechallenge was positive.[740]

Regarding musculoskeletal events, there were no cases of rhabdomyolysis reported in this cohort; there were 2 cases of myopathy reported however follow-up data was not available and thus causality assessment was not performed. Of the 229 cases of myalgia that were followed up, 128 were assessed as probably related to rosuvastatin and 69 possibly related to rosuvastatin. Overall, musculoskeletal events were the most frequently reported adverse event. Where causality assessment was conducted, a high proportion of musculoskeletal events were assessed as probably or possibly related to rosuvastatin.[740]

Regarding hepatic events, follow-up data was available for 101 cases of abnormal LFTs, 19 and 48 of these were assessed as probably or possibly related to rosuvastatin respectively. In addition, one case of autoimmune hepatitis and another case of jaundice, raised alkaline phosphatise and ALT were assessed as possibly related to rosuvastatin.[740]

Regarding renal events, there were 25 cases of raised urea / creatinine, 5 of which were assessed as possibly related to rosuvastatin; there were 7 cases of haematuria, 3 of which were assessed as possibly related to rosuvastatin; 9 cases of proteinuria, one of which were assessed as possibly related to rosuvastatin and another was assessed as probably related to rosuvastatin. Two cases of renal failure were reported although follow-up data was not available for either of these cases.[740]

The fourth study was a retrospective matched cohort study with a follow-up duration of up to 18 months in patients initiating treatment with rosuvastatin compared with other statins.[937] All patients receiving a statin were identified from the administrative database of a large health insurer in the U.S. for the period 1st September 2003 to 29th February 2004. Patients were included in the cohort if they had no prescription for a statin (naïve initiators) or if they had been prescribed a different statin than the index prescription (switcher initiators) during the baseline period defined as 183 days prior to the index date. Only patients who were at least 18 years of age with complete demographic and enrolment information and at least 183 days of complete enrolment before the index date were included. Patients were excluded if they had claims-based diagnoses of myopathy, rhabdomyolysis, renal dysfunction or hepatic dysfunction associated with a hospitalization during the baseline period.[937]

A total of 194 320 patients were identified as having at least one prescription claim for a statin during the defined time period who were either naïve or switcher initiators of a particular statin. Of these patients, 106 926 met the inclusion criteria, 12 217 of which were rosuvastatin initiators and 94 709 were initiated on other statins. Rosuvastatin initiators were matched to other statin initiators by a multivariate technique (propensity score analysis and matching) in order to balance covariate patterns and account for any baseline characteristics of rosuvastatin initiators that differed from other statin initiators in that time period. All analyses were also adjusted by the number of matched

comparators. Thus, 11 249 rosuvastatin initiators were matched to 37 282 other statin initiators (statin used: 54.2% atorvastatin, 21.2% simvastatin, 11.0% pravastatin, 10.6% lovastatin and 3.1% fluvastatin).[937]

Potential incident cases associated with hospitalization for myopathy, rhabdomyolysis, renal dysfunction, or hepatic dysfunction and in-hospital death were identified from health insurance claims and data on 403 (81%) of these potential outcomes were successfully abstracted from written medical records with 125 (31%) cases of outcome incidence being confirmed.[937]

Incidences of adverse events were low. Five cases of rhabdomyolysis or myopathy were found among 43 585 person-years for the entire study cohort (Incidence Rate = 1.15 per 10 000 person-years (95% CI 0.37 to 2.68)). Adjusted Hazard Ratios were calculated and it was found that there were no significant differences between those initiated on rosuvastatin compared with those initiated on other statins for any outcome measure (HR = 1.98 (95% CI 0.18 to 21.90) for rhabdomyolysis, HR= 0.90 (95% CI 0.47 to 1.73) for renal dysfunction, HR not calculable for myopathy, HR=0.87 (95% CI 0.18 to 4.14) for hepatic dysfunction and HR=0.51 (95% CI 0.24 to 1.10) for in-hospital death).[937]

The fifth study reviewed adverse event reports (AERs) to the Food and Drug Administration USA (FDA) to determine the frequency of rosuvastatin-associated events relative to other commonly used statins, namely; atorvastatin, simvastatin, pravastatin and cerivastatin (for cerivastatin during the time it was available). Two comparative primary analyses were performed. For the first analysis, AERs were determined for the first year during which rosuvastatin was available in the USA (October 2003 to September 2004) and these AERs were compared with the concomitant time period for the other statins (defined as 'concurrent time period analysis'). The mean doses of statins during this time period was as follows; rosuvastatin 16.7±1.2 mg, simvastatin 53±2.8 mg, pravastatin 18.8±2.0 mg and atorvastatin 21.8±1.4 mg. The second analysis was performed to address the potential of preferential reporting of adverse events with newly marketed drugs. Thus rates of rosuvastatin-associated AERs were compared with those during the first year of marketing for atorvastatin (1997), simvastatin (1992), pravastatin (1992) and cerivastatin (1998). This was defined as 'first year of marketing analysis'. The rates of AERs were calculated as AERs per million prescriptions for various AERs associated with each of the statins.[79]

For the concurrent time period analysis, the rate of rosuvastatin AERs (a composite of rhabdomyolysis, proteinuria / nephropathy, or renal failure) was higher than AERs for simvastatin ($P < 0.001$), pravastatin ($P < 0.001$) and atorvastatin ($P < 0.001$). For the first year of marketing analysis the rate of rosuvastatin-associated composite AERs was not significantly different than simvastatin AERs, but was significantly higher compared with pravastatin ($P < 0.001$) and atorvastatin ($P < 0.001$). Compared with AERs for cerivastatin during its first post marketing year, rosuvastatin composite AERs were less frequent ($P < 0.001$). Sixty two percent of rosuvastatin-associated AERs occurred at doses of ≤ 10 mg / day, and occurred earlier after the initiation of therapy (within the first 12 weeks) compared to other statins. There was no gender predominance. While fatalities were rare, most composite AERs listed hospitalisation as an outcome.[79]

The increased rate of rosuvastatin-associated AERs relative to the other statins was also observed in secondary analysis.

For the concurrent time period analysis, the rate of rosuvastatin-associated AERs for any adverse event was higher than that observed for simvastatin, pravastatin and atorvastatin ($P < 0.001$ all statins versus rosuvastatin). Likewise for serious AERs (life threatening or requiring hospitalisation), liver AERs, muscle AERs without rhabdomyolysis and also renal failure AERs, rosuvastatin had higher rates of adverse events ($P < 0.001$ all statins versus rosuvastatin). Furthermore, rhabdomyolysis AERs, although rare, were also higher for rosuvastatin (simvastatin; $P < 0.01$, pravastatin and atorvastatin; $P < 0.001$).[79]

For the first year of marketing analysis the rate of rosuvastatin-associated AERs was similarly higher for the following AERs compared with other statins; all AERs (simvastatin, pravastatin atorvastatin, cerivastatin P < 0.001 all statins versus rosuvastatin), muscle AERs without rhabdomyolysis (simvastatin, pravastatin atorvastatin, cerivastatin P < 0.001 all statins versus rosuvastatin). Liver AERs were higher for rosuvastatin compared with simvastatin, pravastatin and atorvastatin, but were not significantly different with the rate observed with cerivastatin. Serious AERs were higher for rosuvastatin compared with pravastatin and atorvastatin (P < 0.001 for both); however, the rosuvastatin rate was lower than that observed for simvastatin (P < 0.001) and cerivastatin (P < 0.01). Rosuvastatin was also significantly more likely than simvastatin, pravastatin and atorvastatin to be associated with reports of rhabdomyolysis (P < 0.001 all statins versus rosuvastatin), but compared with the first year of cerivastatin, the rate of rosuvastatin rhabdomyolysis events was significantly less (P < 0.001). Finally, the rate of rosuvastatin-associated renal failure AERs was higher compared with pravastatin and atorvastatin (P < 0.001 for both), but similar to that observed with simvastatin and cerivastatin.[79]

There are a number of intrinsic limitations of post marketing adverse event analysis. The analysis is based on reporting rates, not on actual adverse event rates. In clinical practice, adverse events are under reported, and serious adverse events are more likely to be reported than less serious events. The retrospective nature of the analysis does not allow confirmation of causality, or control of potential confounders. For example, providers tend to report preferentially adverse events with newly marketed drugs. In addition, certain adverse events may not be recognised as related to a particular class of drug. Post marketing analysis can also be influenced by publicity, favourably or unfavourably. Another time dependent post marketing variable could be related to the availability of drug dosage. In this context, the relatively low rate of atorvastatin-associated AERs during its first year of marketing may be partially attributable to the fact that only the 10 mg dose was available in the first year.[79]

Not with standing these limitations, the review found that rosuvastatin had a higher rate of AERs compared with other commonly prescribed statins based upon adverse event reports to the FDA. The authors of the review stated that the reported occurrence of these AERs early after initiation of therapy (within 12 weeks on average) suggests that vigilant monitoring for adverse events may ameliorate the risk of toxicity when rosuvastatin is used. They also stated that it would seem prudent for healthcare providers to consider other statins as first line therapy, to initiate rosuvastatin therapy in appropriate patients at lower doses as well as careful monitoring for adverse events.[79]

Q.40.11 Evidence to recommendations – statins

The NICE technology appraisal on statins[1007] considered twenty-eight randomised controlled trials of statins in adults with or at risk of CVD.

No studies that reported cardiovascular events as outcomes were identified for rosuvastatin. Fourteen placebo-controlled studies in which all participants had CHD at study entry were identified for inclusion in a meta-analysis. There were significant reductions in all cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), nonfatal MI (RR 0.69, 95% CI 0.59 to 0.95), new or worsening intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91). There was no significant reduction in stroke mortality (RR 1.07, 95% CI 0.67 to 1.71) or TIA (RR 0.66 95% CI 0.37 to 1.17). The relative effectiveness of statins did not differ by sex, in people with and without diabetes, or in people over 65 years compared with younger people. For secondary CHD prevention the incremental cost per QALY ranged from £10,000 to £16,000 for all age groups with little difference for men and women.

The NICE technology appraisal[1007] recommended statin therapy for all adults with clinical evidence of CVD and that when the decision has been made to prescribe a statin, it is recommended that therapy

should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose). The GDG considered that for initiation of treatment, simvastatin 40 mg was the most effective drug with a low acquisition cost in secondary prevention.

Q.40.12 The use of higher intensity statins and cholesterol targets

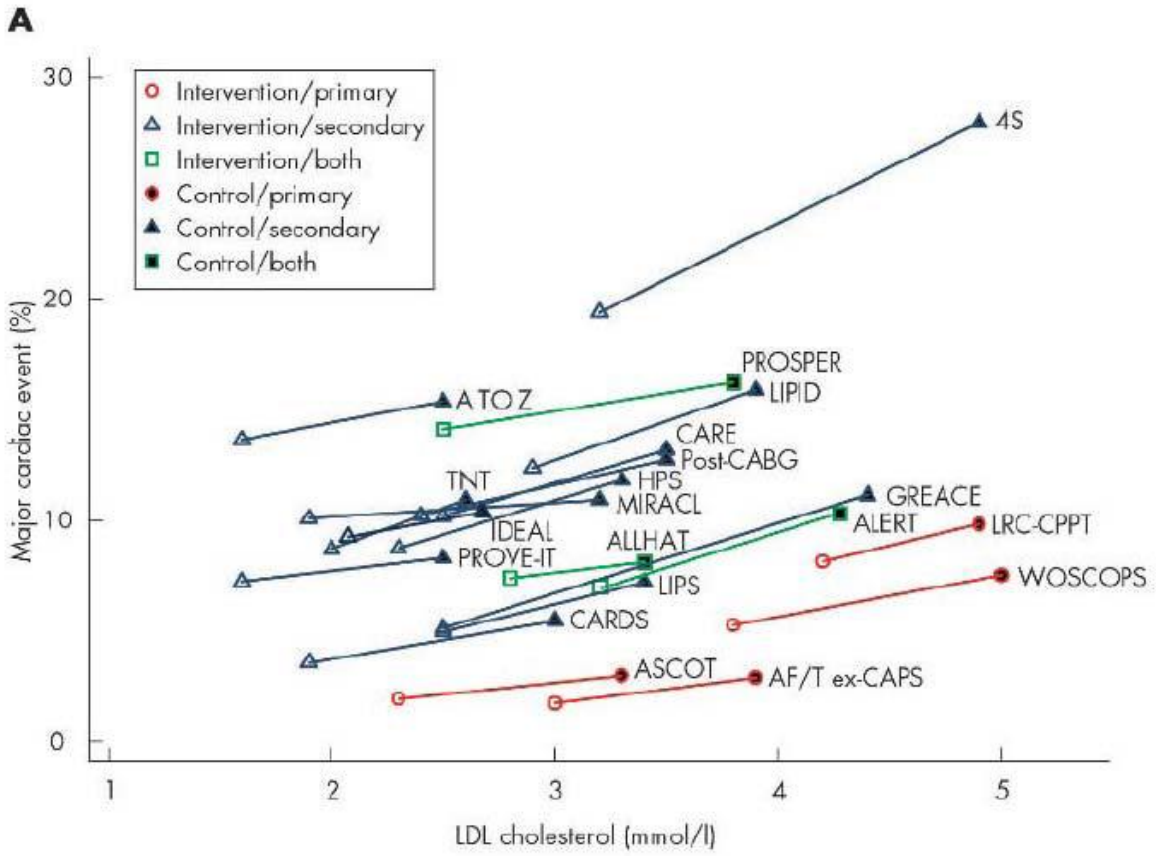
International and national guidelines on lipid lowering for CVD prevention have all defined goals or targets of therapy. These target levels have become progressively lower over time and differ between guidelines. The Joint British Societies first recommended in 1998 a total cholesterol target of less than 5.0 mmol/l and an LDL cholesterol target of less than 3.0 mmol/l, or a 25% total cholesterol reduction or a 30% LDL cholesterol reduction, whichever is greater[15]. The National Service Framework for CHD in 2000 recommended levels less than total cholesterol 5 mmol/l or LDL cholesterol 3 mmol/l (or a 25% TC reduction or 30% LDL cholesterol reduction whichever is greater) and these remain the current national advice (DoH March 2000 website). In 2003 the Joint European Societies Task Force on CVD Prevention recommended a total cholesterol level less than 4.5 mmol/l and LDL cholesterol levels below 2.5 mmol/l. Since 2004 in the USA high risk CVD patients are advised to achieve LDL cholesterol levels below 1.81 mmol/l.[1006] The most recent Joint British Societies 2005 guideline recommended target levels below total cholesterol 4 mmol/l and LDL cholesterol 2 mmol/l (or a 25% reduction in total cholesterol and a 30% reduction in cholesterol if that yields a lower value).[1445] More recently the Scottish Sign Guideline 2007 considered total cholesterol targets of 4 mmol/l or 4.5 mmol/l would have major resource implications for NHS Scotland[1221], but this was not based on a formal cost-effectiveness analysis. SIGN recommended that pending further studies on mortality, safety, and cost-effectiveness, a total cholesterol target of less than 5 mmol/l in individuals with CVD should be a minimum standard of care.[1221]

The Cholesterol Trialists Collaboration[131] reported an approximately linear relationship between the absolute reductions in LDL cholesterol achieved 14 statin trials and the proportional reductions in the incidence of coronary and other events. The authors of the Cholesterol Trialists Collaboration state that there is a significant trend towards greater proportional reductions in major coronary events being associated with greater mean absolute LDL cholesterol reductions in the different trials.[131] There was no significant heterogeneity between the relative effects after weighting for the absolute LDL cholesterol reduction.[131] They found that the proportional reduction in the event rate per mmol/l reduction in LDL cholesterol was largely independent of the presenting cholesterol level. So, lowering the LDL cholesterol level from 4 mmol/l to 3 mmol/l reduced the risk of vascular events by about 23% and lowering LDL cholesterol from 3 mmol/l to 2 mmol/l also reduced residual risk by about 23%. There is a near linear relationship between the log of the risk and cholesterol reduction, but it is important to appreciate that although the relative risk reduction remains constant, at lower cholesterol levels there is a smaller absolute reduction in cardiovascular events, and it is absolute risk reduction that determines cost-effectiveness.

This log linear relationship describes the effect of cholesterol lowering with statins, at least down to a LDL cholesterol of 2 mmol/l. A meta-analysis of higher intensity statins[266] confirmed that the observed 0.67 mmol/l reduction in LDL cholesterol would be expected to lead to a 14% reduction in cardiovascular events on the basis of the log linear hypothesis and the observed reduction of 16% was consistent with this.

The majority of randomised controlled trials to date have not shown a reduction in LDL cholesterol below 2 mmol/l with statin therapy (Figure 1, JBS2 [1445]). LDL cholesterol was reduced below an average value of 2 mmol/l in only three of the twenty trials shown; PROVE-IT 1.6 mmol/l[265], A-Z 1.7 mmol/l[398], MIRACL 1.9 mmol/l.[1219] These are all recent randomised controlled trials at maximal licensed statin dosage. These trials had strict recruitment criteria and patients with higher levels of LDL cholesterol tended to be excluded, and are not representative of the general population with CVD. Moreover, the reported LDL cholesterol reductions were median values of the trial participants.

Figure 1 Statin trials showing % reduction in major cardiac events and LDL cholesterol (mmol/l)



(Figure from JBS2[1445])

GDG discussion on use of targets

Within the GDG, there were differing views on the use of cholesterol "targets" i.e. levels of total and LDL cholesterol that patients on lipid lowering therapy should either aim to be below or should achieve. Proponents of targets considered that the log linear hypothesis from the Cholesterol Trialists Collaboration[131] supported the use of targets because it confirmed that for LDL cholesterol "lower is better". GDG members were concerned that patients could be potentially under treated if no goal or target were specified. As a proportion of patients can reach cholesterol targets of total cholesterol of less than 4 mmol/l or LDL cholesterol of less than 2 mmol/l on standard doses of statins such as simvastatin 40mg the use of a target would reduce the likelihood that patients would be under-treated with suboptimal doses of statins such as simvastatin 10mg.

Opponents of setting targets raised a number of concerns. There was a minority view within the GDG that any targets are essentially misleading as trials have not treated to target but have used specific drugs to treat patients. For other members of the GDG there was concern as to how targets may be interpreted. Firstly, in practice targets can be interpreted to mean that all patients on treatment should attain the recommended level, irrespective of their starting cholesterol level. This takes no account of the distribution of cholesterol levels in the population prior to commencement of treatment, nor of differing responses to treatment and differing adherence to treatment. It is also important to note that the majority of randomised controlled trials which recruited selected

populations did not find statin therapy reduced LDL cholesterol below 2 mmol/l (Figure 1). Opponents of setting targets considered it misleading for both professionals and patients, to set a target that is interpreted as 'should be achieved', knowing that many patients will not achieve this.

Secondly, two-thirds of the gain from a statin is realised by the initial dose. Lower cholesterol levels for individual patients may be achieved by using higher intensity statins but for each doubling of dose there is a smaller absolute reduction in cardiovascular events. There was concern that the adoption of targets may encourage the indiscriminate use of either high dose statins or combination lipid therapy.

Finally, there is no trial evidence that drug combinations such as a statin plus a fibrate, will produce additional cost-effective absolute reductions in cardiovascular events.

The GDG concluded by majority that the use of higher intensity statins or drug combinations should be driven by trial evidence of absolute benefit in clinical outcomes and cost effectiveness, and less by targets and relative risk. The GDG accepted again by a majority that the use of a target figure can be helpful in guiding increases of lipid lowering drugs as long as it is clear that this figure is intended to guide treatment rather than be a figure patients are expected to achieve. The wording of the recommendations was agreed to reflect this.

The GDG agreed using the clinical and cost effectiveness evidence that patients with ACS benefit from immediate high intensity statins. Health economic analyses for this guideline and published literature indicate that high intensity statins are less cost effective for patients with CAD. These patients should start on a standard dose of statin and the target figure used to inform increases in treatment.

The GDG recognised from the health economic modelling that over half of patients with stable CAD will not achieve total cholesterol level of 4 mmol/l and LDL cholesterol of 2 mmol/l when given 80 mg simvastatin. An audit level of total cholesterol 5 mmol/l may help to assess progress in populations and groups.

Table 7 and Table 8 show absolute total and LDL cholesterol reduction and percentage reductions in serum concentrations according to statin and daily dose

Table 7: Absolute LDL cholesterol reduction* and percentage reductions in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

Statin	Daily dose (mg)	Absolute LDL cholesterol reduction (mmol/l) (95% confidence intervals)	Percentage reduction LDL cholesterol in serum
Atorvastatin	10	1.79 (1.62 to 1.97)	37%
Atorvastatin	20	2.07 (1.90 to 2.25)	43%
Atorvastatin	40	2.36 (2.12 to 2.59)	49%
Atorvastatin	80	2.64 (2.31 to 2.96)	55%
Pravastatin	40	1.38 (1.31 to 1.46)	29%
Rosuvastatin	5	1.84 (1.74 to 1.94)	38%
Rosuvastatin	10	2.08 (1.98 to 2.18)	43%
Rosuvastatin	20	2.32 (2.20 to 2.44)	48%

Simvastatin	40	1.78 (1.66 to 1.90)	37%
Simvastatin	80	2.01 (1.83 to 2.19)	42%

- Absolute reductions are standardised to usual LDL cholesterol concentration of 4.8 mmol/l before treatment (mean concentration in trials). Percentage reductions are independent of pre-treatment LDL cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 4.8.

Table 8: Absolute cholesterol reduction* and percentage reductions # in serum total cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

Statin	Daily dose (mg)	Absolute total cholesterol reduction (mmol/l) (95% confidence intervals)	Percentage reduction total cholesterol in serum
Atorvastatin	10	2.15 (1.94 to 2.33)	32%
Atorvastatin	20	2.45 (2.28 to 2.70)	36%
Atorvastatin	40	2.83 (2.54 to 3.11)	42%
Atorvastatin	80	3.17 (2.77 to 3.55)	47%
Pravastatin	40	1.99 (1.88 to 2.10)	29%
Rosuvastatin	5	2.21 (2.09 to 2.33)	33%
Rosuvastatin	10	2.50 (2.38 to 2.62)	37%
Rosuvastatin	20	2.74 (2.64 to 2.93)	40%
Simvastatin	40	2.14 (1.99 to 2.28)	31%
Simvastatin	80	2.41 (2.20 to 2.63)	35%

*Absolute reductions are standardised to usual total cholesterol concentration of 6.8 mmol/l before treatment (mean concentration in trials). #Percentage reductions are independent of pre-treatment total cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 6.8.

Q.41 Fibrates

Q.41.1 Evidence statements for fibrates

Two randomised controlled trials in patients after an MI and / or with angina found that clofibrate therapy was not associated with a reduction in fatal MI or sudden death in people with angina compared with placebo. One trial found that clofibrate therapy was not associated with a reduction in cardiovascular morbidity compared with placebo while the other found that clofibrate therapy was associated with a reduction in the rate of first non-fatal infarct in women with a history of angina

compared with placebo.
One randomised controlled in patients after an MI and / or with angina found that bezafibrate therapy was not associated with a reduction in the composite of fatal MI, non-fatal MI and sudden death compared with placebo. In addition, no benefit was seen for cardiovascular morbidity.
One randomised controlled trial in men after an MI and / or with angina found that gemfibrozil therapy was associated with a reduction in the composite of fatal MI, sudden death, death due to congestive heart failure and death as a complication of invasive cardiac procedures compared with placebo.
Two randomised controlled trials in patients following stroke or TIA found that clofibrate therapy was not associated with a reduction in all cause mortality or cardiovascular morbidity compared with placebo.
One randomised controlled trial in patients with peripheral arterial disease showed that bezafibrate therapy was not associated with a reduction in the combination outcome of fatal and nonfatal CHD events and stroke compared with placebo although bezafibrate therapy was associated with a reduction in the incidence of non-fatal coronary heart disease.

Q.41.2 Clinical effectiveness of fibrates

Seven randomised controlled trials were identified that compared fibrate therapy with placebo in patients with a history of CVD. Four of these were in patients after an MI and / or with angina, two were in patients following a stroke or transient ischaemic attack and one was in patients with peripheral arterial disease.

Four randomised controlled trials were identified in patients after an MI and / or with angina.[183];[1173];[1148];[3]

The first randomised controlled trial[1148] recruited patients aged 40-69 years with a history of angina, MI or both (27% had angina only). A total of 717 patients were randomised to receive either clofibrate or placebo (olive oil) and were followed up for a mean duration of 4 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death, fatal MI or first non-fatal MI compared to placebo.

The second randomised controlled trial[3] recruited patients under 65 years with a history of angina, MI or both (40% had angina only). A total of 497 patients were randomised to receive either clofibrate or placebo (corn oil) and were followed up for 5 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death or fatal MI compared to placebo but was found to decrease the rate of first non-fatal infarct compared to placebo in women with a history of angina ($P < 0.05$) but not men.

Both of these studies used the drug clofibrate which has now been withdrawn from the British National Formulary.

The third randomised controlled trial[1173] recruited men with an HDL cholesterol of 1.0 mmol/l or less, LDL cholesterol 3.6 mmol/l or less and triglycerides less than 3.4 mmol/l with documented coronary artery disease defined as a history of MI, angina, having undergone coronary revascularization, or angiographic evidence of coronary stenosis. Of these, 61% had a prior history of MI. Concomitant drug therapy at the start of the trial was as follows; aspirin 82%, beta blockers 43%, nitrates 46%, ACE inhibitors 21%, calcium channel blockers 53%. Patients were randomised to either gemfibrozil or placebo. Patients were followed for a mean 5.1 years. Gemfibrozil therapy was associated with a reduction in the primary endpoint of a combination of nonfatal MI and death from CHD compared with placebo. The incidence of the secondary outcome of a combination of nonfatal MI, death from

CHD and confirmed stroke was also reduced in the gemfibrozil treatment group compared with the placebo. In addition, gemfibrozil therapy was associated with a reduction in the following outcomes compared with placebo: nonfatal MI, investigator-designated stroke, transient ischaemic attack, carotid endarterectomy and hospitalisation for congestive heart failure. Treatment with gemfibrozil was not associated with any benefit for the following outcomes: death due to coronary heart disease, death from any cause, confirmed stroke, revascularisation, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, peripheral vascular surgery and hospitalisation for unstable angina.

Patients assigned to gemfibrozil had lower total cholesterol and triglycerides levels and higher HDL cholesterol levels compared to patients in the placebo group. LDL cholesterol levels were the same in both groups. Gemfibrozil treatment was associated with a greater incidence of dyspepsia.[1173]

The fourth randomised controlled trial[183] recruited patients with a history stable angina pectoris and / or MI. Of these, 57% had prior angina (and 78% had a history of MI). A total of 3090 patients were randomised to receive either bezafibrate (retard) or placebo and were followed up for a mean duration of 6.2 years. Treatment with bezafibrate did not confer any benefit over placebo for the primary endpoint of a composite of fatal MI, nonfatal MI and sudden death. There was also no benefit observed for any of the individual components of this endpoint. Bezafibrate had no benefit over placebo for the following secondary endpoints: combination of hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft, hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, mortality, cardiac mortality, noncardiac mortality, stroke or ischemic stroke.

Compared with the placebo group, triglyceride levels were lower in the bezafibrate subgroup that had triglyceride levels ≥ 2.26 mmol/l. The overall incidence of any adverse event was 69% in both groups, and the frequency of each type adverse event was similar in both groups.[183]

Two randomised controlled trials were identified that compared fibrate therapy with placebo in patients with a history of stroke or transient ischaemic attack.[58];[4] Both of these trials used clofibrate.

The first randomised controlled trial[58] recruited patients with focal cerebral vascular disease (those with one stroke, multiple strokes or transient cerebral ischaemia) who had a serum cholesterol level of 250 mg /100ml or higher. A total of 95 patients were randomised to receive either clofibrate or placebo and the period of observation was from 4 months to 4 years. Compared with placebo, clofibrate therapy was not associated with a decrease in all cause mortality. Patients assigned to clofibrate had lower levels of serum cholesterol compared to those who received placebo; mean proportional change in serum cholesterol level was -12.69% for control and -21.41% for clofibrate ($P < 0.05$). It should be noted that this was a small study and is likely to be underpowered for the outcomes described.

The second randomised controlled trial[4] recruited male veterans with one or more cerebral infarctions or transient ischaemic attack within the past 12 months. A total of 532 men were randomised to receive either clofibrate or placebo and were followed up for an average duration of 21 months. Compared with placebo, clofibrate therapy was associated with a non significant decrease in all cause mortality: 30/264 deaths occurred in the placebo group versus 22/268 in the group allocated to receive clofibrate. For the outcome of vascular morbidity, there was no difference between the groups in the incidence of MI, TIA or angina. There was an increase in recurrence of cerebral infarction (23/264 placebo versus 37/268 clofibrate) and an increase in the incidence of congestive heart failure (4/264 placebo versus 15/268 clofibrate) in the clofibrate group compared to those receiving placebo but these differences were not tested for statistical significance. All other side effects were similar between groups. Regarding blood lipids, clofibrate decreased triglycerides compared to the control group (29% decrease clofibrate versus a 4% increase control) but had a negligible effect on cholesterol levels. Again, no statistical analysis was performed so the significance

of these results is unknown It should be noted that this was a small study and is likely to be underpowered for the outcomes described.

One randomised controlled trial was identified that compared fibrate therapy with placebo in patients with a history of peripheral arterial disease.[950] This trial recruited men with lower extremity arterial disease, 24% had stable angina, 21% had a previous MI and 12% had a history of stroke. A total of 1568 men were randomised to receive either bezafibrate (as Bezalip mono) or placebo and were followed up for a mean of 4.6 years. Bezafibrate therapy did not confer any benefit over placebo for the primary endpoint of a composite of CHD events (both fatal and non-fatal) and all strokes. When the individual endpoints were analysed separately, bezafibrate had no benefit over placebo for the primary outcome of a composite of CHD events and all strokes, but was associated with a reduction in the incidence of non-fatal CHD events (RR 0.60, 95% CI 0.36 to 0.99).

Q.41.3 Cost-effectiveness of fibrates

There were no cost-effectiveness studies found on the use of fibrates compared with placebo in secondary prevention of CVD.

Q.41.4 Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

Q.42 Nicotinic acids

Q.42.1 Evidence statements for nicotinic acids

No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or following stroke.
One randomised controlled trial in patients after MI found that nicotinic acid therapy was associated with a reduction in non-fatal MI and the combination of coronary death or non-fatal MI compared with placebo. Nicotinic acid therapy was not associated with a reduction in all cause mortality, cardiovascular mortality or cardiovascular morbidity compared with placebo.

Q.42.2 Clinical effectiveness of nicotinic acids

No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or following stroke. Due to the lack of trial evidence, it was decided by the GDG to consider evidence used in the NICE Myocardial Infarction guidance (Myocardial infarction - Secondary prevention in primary and secondary care for patients following a myocardial infarction, CG48, 2007)

One paper was identified that compared niacin treatment with placebo in patients after an MI.[6]f The Coronary Drug Project Research Group randomly assigned post MI patients to six treatment groups: low and high conjugated oestrogen therapy, clofibrate, dextrothyroxine sodium, niacin and a placebo. The oestrogen and dextrothyroxine arms were stopped early because of an excess of nonfatal cardiovascular events and death, respectively. Patients were followed for 5 years.

Compared with placebo, niacin was not associated with a reduction in the incidence of the following outcomes: all cause mortality, the individual components of all cause mortality, definite pulmonary embolism (fatal or nonfatal), fatal or nonfatal stroke or intermittent cerebral ischaemic attack, definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis and also any

definite or suspected fatal or nonfatal cardiovascular event. Niacin therapy reduced the incidence of nonfatal MI and also the combination of coronary death or nonfatal MI, compared with placebo. Cholesterol and triglycerides levels decreased in the niacin group compared with the placebo group.

Patients in the niacin group had a greater incidence of the following side effects compared with the placebo group: the combination of diarrhoea, nausea, vomiting, black tarry stools, stomach pain, flushing, itching of skin, urticaria, other type of rash, pain or burning when urinating, decrease in appetite, unexpected weight loss, and excessive sweating[6]

Q.42.3 Cost-effectiveness of nicotinic acids

There were no cost-effectiveness studies found on the use of nicotinic acids compared with placebo in secondary prevention of CVD.

Q.42.4 Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of nicotinic acids as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

Q.43 Anion exchange resins

Q.43.1 Evidence statements for anion exchange resins

No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity.
One small randomised controlled trial in patients with a history of CVD found that cholestyramine therapy was associated with a reduction in total cholesterol and LDL cholesterol compared with placebo.

Q.43.2 Clinical effectiveness of anion exchange resins

No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity.

One small randomised controlled trial was identified on the clinical effectiveness of anion exchange resins compared with placebo to improve lipid level profiles in patients with coronary artery disease.[213] This trial recruited people with elevated LDL cholesterol and angiographic evidence of coronary artery disease (50% of whom had symptomatic angina and / or MI). A total of 143 patients were randomised to receive either cholestyramine 24 g per day or placebo and were followed up for five years. Treatment with cholestyramine resulted in decreases in total and LDL cholesterol compared with placebo (5 year mean lipid level differences were - 0.1 mmol/l placebo versus - 1.4 mmol/l cholestyramine ($P < 0.001$) for total cholesterol and - 0.26 mmol/l placebo versus - 1.66 mmol/l cholestyramine ($P < 0.001$) for LDL cholesterol). Cholestyramine therapy did not have an effect on triglycerides or HDL cholesterol. There were negligible differences between groups for the ancillary outcomes of mortality and morbidity.

Q.43.3 Cost-effectiveness of anion exchange Resins

There were no cost-effectiveness studies found on the use of anion exchange resins compared with placebo in secondary prevention of CVD.

Q.43.4 Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

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