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

Methods, evidence and recommendations

July 2014

Final version

Commissioned by the National Institute for Health and Care Excellence

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Update information

December 2023: NICE's original guideline on lipid modification (CG181, July 2014) has been updated and replaced by NICE guideline NG238. We reviewed the evidence and made a new recommendation on the target lipid level for secondary prevention of CVD for adults on lipid-lowering treatment. We also restructured the guideline to provide better navigation.

May 2023: NICE's original guideline on lipid modification was published in 2014. The following sections have been replaced by the 2023 update:

- section 6 on full formal risk assessment of CVD risk
- section 8 on cardioprotective diet
- section 11 on statins for the primary and secondary prevention of CVD (except section 11.10 on adherence to statin therapy).

See the NICE website for the guideline recommendations and the evidence reviews for the 2023 update. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2023.

Contents

Guideline update

This guidance is a partial update of NICE clinical guideline 67 (published 2008) and will replace it.

New and updated recommendations have been included covering lipid modification management and CVD risk assessment.

Recommendations are marked to indicate the year of the last evidence review [2008] if the evidence has not been updated since the original guideline, [2008, amended 2014] if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation, [2014] if the evidence has been reviewed but no change has been made to the recommendation and [new 2014] if the evidence has been reviewed and the recommendation has been added or updated. You are invited to comment only on the new and updated recommendations in this guideline.

Old evidence reviews and recommendations from the 2008 guideline are shaded pink with '2008' in the right hand margin.

Appendix O contains recommendations from the 2008 guideline that NICE proposes deleting in the 2014 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where there are replacement recommendations, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given.

The original NICE guidance and supporting documents are available from:

http://guidance.nice.org.uk/CG67

Guideline Development Group

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2008

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2008

Acknowledgements [2014]

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We would like to offer our condolences to the family of Eleanor Grey. Eleanor died during the development of this guideline. She brought her professional and personal experience to the guideline and helped to ensure that people receiving care from the NHS were always at the centre of consideration.

Acknowledgements [2008]

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- The expert reviewers who took the time to comment on Dr Marshall's paper:
- Dr Peter Jackson
- Prof Paul Durrington
- Dr Tim Holt
- Prof Rod Jackson
- Mrs Margaret May
- Prof Tim Reynolds

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- Miss Alison Mead, Dietitian co-optee
- Dr Kiran Patel, Expert on CVD risk and ethnicity co-optee
- Dr Nadeem Qureshi, Expert peer reviewer family history
- Dr Dermot Neely, Lipids expert co-optee
- Dr Jane Skinner, MI Expert
- The staff at NICE who have helped us with this guideline in particular Dr. Phil Alderson, Sarah Willet and Colette Marshall.
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- Prof Alistair Gray for his contribution to the economic models.

2008

1 Introduction

1.1 Background

Cardiovascular disease (CVD), which comprises coronary heart disease (CHD) and stroke, is one of the most significant causes of death in England and Wales, accounting for almost one third of deaths.[262,262] In 2010 180,000 people died from CVD with about 80,000 death due to CHD and 49,000 due to strokes. Of these deaths, 46,000 occurred before the age of 75 years and of those, 70% were in men. The epidemic of CVD is caused by the process of atherosclerosis. Atherosclerosis is an age-dependent process affecting blood vessel (vascular) walls driven by environmental and genetic risk factors in which lipid (including cholesterol)-laden macrophages play a key role.[249,249] The environmental risk factors that have driven the epidemic of CVD include smoking, diets high in calories, saturated fats, carbohydrate and salt, allied with low fruit and vegetable intakes, whose effects have been exacerbated by sedentary lifestyles.[289,290] The epidemic of CVD peaked in the 1970s and 1980s and death rates have more than 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 has a high rate of CVD compared to other European countries. 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, and that drug treatment, including secondary prevention, accounts for the remaining 40% of the decline in mortality.[263,263] Since 2000, immediate fatal CVD deaths have halved. CHD rates have fallen more rapidly in older compared to younger groups, with an approximately 50% reduction in people aged 55–64 compared with a 20% reduction in men aged 35–44 but no reduction in women aged 35–44. 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 in England almost £6940 million in 2003, rising to £7880 million in 2010.[199,199]

CVD shows a strong age dependence and predominantly affects people over 50 years. Risk factors for CVD include non-modifiable factors such as age, gender, family history of CVD, ethnic background and modifiable risk factors include smoking, raised blood pressure and cholesterol. 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.

1.2 Management of CVD risk

The importance of CVD as a cause of morbidity and mortality in the UK led to the publication of the report 'Our Healthier Nation' in 1999 and promulgation of a National Service Framework for CVD in 2001. A target was set of a 40% reduction in CVD death by 2010, allied with a reduction in inequalities in CVD rates across the UK. These were achieved by 2008-2009.[262,262] Given the still substantial burden of CVD, the National Service Framework was updated in 2013 by the NHS Cardiovascular Disease Outcomes Strategy.[70] This advised local authorities, NHS commissioners and providers on how to improve CVD outcomes in their localities. The CVD Outcomes strategy recommends:

- reducing premature mortality rates for CVD by improving prevention, diagnosis and treatment, bringing all services up to the standards of the best
- managing CVD as a single family of diseases and develop a standardised template for community and hospital care
- supporting better identification of families or individuals at high risk of CVD and improve its management in primary care
- improving intelligence, monitoring and research into CVD and publication of comparative data on the quality of care provided for patients with CVD.

The 10 actions suggested in the strategy address different aspects of the burden of CVD.

Within CVD prevention, actions include interventions to reduce the prevalence of CVD risk factors in the general population, as most CVD events occur in the large group in the population at low individual risk. Smoking cessation combined with reductions in mean blood pressure and cholesterol through nationwide reductions in calorie intake, salt intake, saturated fat consumption and increased physical activity are fundamental to the national strategy for health improvement.

The second group of interventions aim to identify individual people at high risk of developing CVD, and then focus health service resources on those at greatest risk and hence with most to gain. This strategy, largely based in primary care, involves assessment of those at high risk through the NHS Health Check programme[71] and interventions including smoking cessation and appropriate advice on diet, physical activity and if necessary treatment for high blood pressure and cholesterol. The Health Check programme aims to prevent 1600 CVD events per year. However, audits of national and international practice show there is still room for improvement.[136,137]

The third group of interventions focus on people with established CVD (secondary prevention) which includes modification of lipid profiles amongst other interventions. Despite current interventions, national and international audits show that though performance is improving,[135,136] many of these patients do not receive optimal care.[136,136]

These programmes include lipid modification as part of the strategy for CVD risk management. Though many lipid-lowering therapies have been developed,[249,249] the singular successes achieved with statin therapy mean that these agents form the first-line therapy for pharmacological intervention on lipid profiles.[249,250] The action of statins highlights the key nature of reductions in serum low-density lipoprotein (LDL) cholesterol as a marker of an underlying mechanism to reduce CVD events.[249,249] Statin therapy requires long-term treatment to achieve its benefits. One of the key challenges in the field of CVD prevention is to improve adherence in patients who have experienced CVD events, and how to convince people who feel well that they need to make substantial lifestyle changes or that they may require lifelong drug treatment. This requires high quality information and communication on the benefits and risks associated with these therapies.

This guideline updates for primary prevention, the NICE technology appraisal, 'Statins for the prevention of cardiovascular events' (TA94, 2007) and reviews and updates the recommendations made in the NICE guideline Lipid Modification (CG67, 2008) for primary and secondary prevention of CVD. 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 CVD. The guideline development group wishes to make clear that lipid modification should take place as part of a programme of risk reduction which also include attention to the management of all other known CVD risk factors.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence
- the ‘NICE guideline’ lists the recommendations
- ‘information for the public’ is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline was:

To develop a partial update of:

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

This update was undertaken as part of the guideline review cycle.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Anthony Wierzbicki in accordance with guidance from NICE.

The group met every 5-8 weeks during the development of the guideline. At the start of the guideline development process, all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

(a) What this guideline covers

Risk assessment and prevention of CVD disease in the following populations:

- Adults (aged 18 years and older) without established CVD.
- Adults with type 1 diabetes (not covered in the original guideline).
- Adults with type 2 diabetes (not covered in the original guideline).
- Adults with chronic kidney disease (CKD) (not covered in the original guideline).
- Adults (aged 18 and older) with established CVD.
- 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.

For further details please refer to the scope in Appendix A and protocols in Appendix C.

(b) What this guideline does not cover

Risk assessment and prevention of CVD disease in the following populations:

- Children and young people (aged 18 years and younger)
- People with familial hypercholesterolaemia.
- People with familial clotting disorders that increase cardiovascular risk.
- People with other genetic disorders that increase cardiovascular risk.
- People at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes other than diabetes.
- People receiving renal replacement therapy.

(c) Relationships between the guideline and other NICE guidance

NICE Technology appraisals to be updated by this guidance:

- Statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94, 2006).

Related NICE Technology appraisals:

- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007).
- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007).
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006).

Related NICE Clinical guidelines:

- Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guidance CG67 (2008).
- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Medicines adherence. NICE clinical guidance 76 (2009).
- Myocardial infarction: secondary prevention. NICE clinical guideline 172 (2013).
- Myocardial infarction with ST-segment elevation. NICE clinical guideline 167 (2013).
- Lower limb peripheral arterial disease. NICE clinical guideline 147 (2012).
- Familial hypercholesterolaemia: identification and management of familial hypercholesterolaemia. NICE clinical guideline 71 (2008).
- Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline 66 (2008).
- Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006).
- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). [Replaced by NICE clinical guideline 127]

Related NICE Public health guidance:

- Preventing type 2 diabetes - risk identification and interventions for individuals at high risk. NICE public health guidance 38 (2012).
- Reducing the rate of premature deaths from cardiovascular disease and other smoking-related diseases: finding and supporting those most at risk and improving access to services. NICE public health guidance 15 (2008).
- 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).
- 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).

- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance 1 (2006).

Related NICE guidance currently in development:

- Chronic kidney disease (update). NICE clinical guideline. Publication expected July 2014.
- Type 1 diabetes (update). NICE clinical guideline. Publication expected August 2015.
- Type 2 diabetes (update). NICE clinical guideline. Publication expected August 2015.

3 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2012[190].

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews. Prognostic questions were developed in a framework of population, presence or absence of factors under investigation (for example prognostic factors) and outcomes.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical issues identified in the scope (Appendix A).

A total of 11 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions and outcomes

Chapter	Title	Type of review	Review question	Outcome
14	Bile acid sequestrants	Intervention	What is the clinical and cost effectiveness of bile acid sequestrants (anion exchange resins) versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	All-cause mortality CV mortality Sudden cardiac death Myocardial infarction Stroke or TIA Hospitalisation Adverse events Quality of life
6	CVD risk assessment tools	Prognostic	Which risk assessment tools are the most accurate and cost effective for predicting the risk of CVD events in adults without established CVD (primary prevention) and without diabetes?	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: D statistic, R^2 statistic and Brier score Reclassification
6	CVD risk assessment tools	Prognostic	Which risk assessment tools are the most accurate and	Area under the ROC curve (c-index,

Chapter	Title	Type of review	Review question	Outcome
			cost effective for predicting the risk of CVD events in adults without established CVD (primary prevention) and with diabetes?	c-statistic) Sensitivity Specificity Predictive values at 5%, 10%, 15% and 20% threshold Predicted risk versus observed risk (calibration) Other outcomes: D statistic, R^2 statistic and Brier score Reclassification
8	Dietary interventions	Intervention	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)?	All-cause mortality CV mortality Non-fatal MI Stroke Quality of life
11	Efficacy of statin therapy: statins versus placebo and head to head comparisons	Intervention	What is the clinical and cost effectiveness of statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	All-cause mortality CV mortality Non-fatal MI Stroke Quality of life Adverse event: Rhabdomyolysis (CK >10 times normal limit) Adverse event: Myalgia Adverse event: Liver (transaminases >3 times normal limit) Adverse event: New-onset diabetes
12	Fibrates	Intervention	What is the clinical and cost effectiveness of fibrates versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	All-cause mortality CV mortality Sudden cardiac death Myocardial infarction Stroke or TIA Hospitalisation Adverse events Quality of life
10	Foods enriched with phytosterols (plant stanols and sterols)	Intervention	What is the clinical and cost effectiveness of foods enriched with phytosterols	All-cause mortality CV mortality Non-fatal MI

Chapter	Title	Type of review	Review question	Outcome
			(plant stanols and sterols) or phytosterol supplements versus placebo for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	Stroke Quality of life
11.10	Interventions to improve adherence to statin therapy	Intervention	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)?	Adherence Quality of life
13	Nicotinic acids	Intervention	What is the clinical and cost effectiveness of nicotinic acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	All-cause mortality CV mortality Sudden cardiac death Myocardial infarction Stroke or TIA Hospitalisation Adverse events Quality of life
15	Omega-3 fatty acids	Intervention	What is the clinical and cost effectiveness of omega-3 fatty acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?	All-cause mortality CV mortality Sudden cardiac death Myocardial infarction Stroke or TIA Hospitalisation Adverse events Quality of life
11.11	Statins: Predictors of adverse events	Observational	Who is at risk of adverse effects from statin treatment? (Are some subgroups at different risk of adverse events?)	Rhabdomyolysis (CK>10 times normal limit) Myalgia Liver (transaminases>3 times normal limit) New-onset diabetes

(a) Abbreviations: CVD; cardiovascular disease, MI; myocardial infarction, TIA; transient ischaemic attack

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2012.[205] Databases were searched using relevant medical subject headings and free-text terms. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library, and were updated for the final time on 11 November 2013. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

3.2.2 Health economics literature search

Systematic searches were also undertaken to identify relevant health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to CVD in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2010, to ensure recent publications that not yet been indexed by the economic databases were identified. This was supplemented by an additional search that looked for economic papers specifically relating to fibrates, bile acid sequestrants, nicotinic acids, omega-3 fatty acids, or phytosterols and phytostanols on the same databases. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economics search strategies are included in Appendix F. All searches were updated on 11 November 2013. No papers published after this date were considered.

3.3 Evidence of effectiveness

3.3.1 Overview of reviewing the evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual.[205]
- Key information was extracted on the study's methods and PICO factors and results were presented in evidence tables (Appendix G).

- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
  - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
  - Prognostic studies: data were presented as a range of values including; sensitivity and specificity at various thresholds, coupled values of sensitivity and specificity summarised in Receiver Operating Curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively, area under ROC curve (AUC) (as reported by the authors), and ratio of predicted versus observed events. Meta-analyses could not be conducted because the studies reported data at various thresholds.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Figure 1: Step-by-step process of review of evidence in the guideline

3.3.2 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The guideline population encompassed adults aged 18 or older in the following groups;

- People at high risk of CVD (primary prevention population)

- People with type 1 diabetes mellitus
- People with type 2 diabetes mellitus
- People with chronic kidney disease
- People with CVD including people with prior MI, prior stroke, peripheral arterial disease, angina (secondary prevention population)

Evidence was also sought and included for the following special groups for each review question;

- People from black and minority ethnic groups
- People with a family history of CVD
- People from low socioeconomic groups
- People older than 75 years
- Women
- People with autoimmune disease
- People with serious mental illness

Randomised trials, non-randomised trials, and observational studies (including prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if either no other full publication was available for that review question or if the GDG considered the abstract sufficiently important to inform recommendations. One abstract of a published study which reported additional outcomes was included in the review of nicotinic acids.

The search for the review of efficacy of statin therapy identified a systematic review that the GDG considered relevant to the question. The GDG decided that further data were required to inform recommendations and the authors contacted for the information.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C. Excluded studies by review question (with their exclusion reasons) are listed in Appendix J.

3.3.3 Methods of combining studies

3.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate pooled risk ratios (relative risk) for binary outcomes.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation (SD)) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling mean differences, and where the studies had different scales, standardised mean differences were used. A generic inverse variance option in Review Manager was used if any studies reported solely the summary statistics and 95% confidence interval (or standard error); this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics: p-values or 95% confidence intervals (95% CI); meta-analysis was then undertaken for the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies that

summarised results by presenting medians (and interquartile ranges), or only p-values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Stratified analyses were predefined for the majority of questions at the protocol stage according to population; primary prevention, type 1 diabetes mellitus, type 2 diabetes mellitus, chronic kidney disease and secondary prevention. The GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions could be expected to have a different effect.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ and the I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out sensitivity analyses. Pre-specified groups were defined for the review question on efficacy of statin therapy. These included: intensity of statin therapy, population, length of follow-up and specific drug and dose.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

3.3.3.2 Data synthesis for prognostic reviews

Meta-analyses could not be conducted for the review question on risk assessment because the studies reported data at various thresholds. The GDG decided that the results for each risk tool and outcome should be presented separately. The GDG used the results from prognostic studies and a health economic model to decide the clinically acceptable thresholds for the review question on statin therapy.

3.3.4 Types of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were not included. If the GDG believed RCT data would not be appropriate or there was limited evidence from RCTs, best available quality non-randomised studies were to be included (Please refer to Appendix F for full details on the study design of studies selected per review question). For example, case series were the option of study design for the review question on prediction of statin adverse effects.

For the prognostic reviews on risk assessment tools, outcomes were extracted for each study and meta-analysis was not conducted.

3.3.5 Types of analysis

Estimates of effect from individual studies were based on available case analysis (ACA): that is, analysing only data that were available for participants at the end of follow-up, without making any imputations for missing data. The GDG recorded several potential reasons for people dropping out before trial completion:

- adverse effects
- lack of concordance (adherence)

- investigator's discretion (this is usually not defined in the studies but is likely to include clinical or laboratory-determined adverse events, or laboratory abnormalities meaning the drug may be contraindicated, or development of mutations).

The ACA method was used rather than an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data was not available, and furthermore assuming that those with missing outcome data have the same event rate as those who continue. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality. Using ACA, we avoided incorrectly weighting studies in meta-analysis by using a denominator that does not reflect the true sample size with outcome data available. If there was a differential missing data rate between the 2 arms in a study greater than 10%, a sensitivity analysis was performed to determine whether the size and direction of effect would be changed by using an ITT or ACA analysis and whether there was an impact on the meta-analysis. If this were the case, a footnote was added to the GRADE tables to describe the dependence on the assumptions, and results from both ACA and ITT analyses were presented in the forest plots section (Appendix I). However, the majority of trials included in the review of evidence for this guideline (98%) had less than 5% differential missing outcome data.

When the studies reported only ITT results (through imputation), and the number of events was larger than the number of completers in the trial (ACA), then we used the proportion of events from the ITT numbers to derive the number of events for the final sample size of completers. In the cases where it was not possible to extract data from the studies on ACA and authors reported only an ITT analysis, then the results of this analysis was included and a footnote was added to the GRADE tables.

3.3.6 Predictive test accuracy and discrimination for risk assessment tools

We wished to know how accurate the risk stratification tools are in predicting CVD outcomes. This means we want to know across a population if:

- a high risk score in an individual is reflected in a CVD event occurring in that same individual over the next 10 years
- a low risk score in an individual is reflected in freedom from CVD events in that same individual over the next 10 years.

This is very similar, in principle, to how we look at the accuracy of diagnostic tests and we take an analogous approach here, using the term 'predictive test accuracy'. Accordingly, we can use similar methods to determine predictive test accuracy statistics and similar quality assessments to diagnostic test accuracy. There are however some important differences, mainly related to the time dependence of prognosis, including the play of chance (that is, the fact that the event is yet to happen when we measure risk) and these mean we have to modify our quality assessment and to carry out additional analyses to truly answer these types of question (see below).

By analogy with diagnostic test accuracy, we considered the risk tool as the 'index test' and the outcome (observed CVD event) as the 'reference standard'. We can also record pseudo 2×2 tables and calculate sensitivity and specificity, but doing this simplistically means we lose the time-to-event nature of the analysis. To calculate the sensitivity and specificity we have to define the cut-off threshold for high and low risk – and this may be difficult to do because it is often related to treatment thresholds.

Partly to overcome this dilemma, authors have used risk stratification tools to calculate the area under the receiver operating characteristics (ROC) curve (abbreviated to area under the curve – AUC). The ROC curve is a curve fitted to the set of combinations of sensitivity and (1–specificity), across all possible (theoretical) cut-off points. The AUC is actually calculated using alternative computational methods that also allow for the time-to-event nature of the CVD data.

AUC (and its 95% confidence interval), a measure of discrimination, was a common outcome reported by the studies. AUC is not a good method of discriminating between risk stratification tools because it is very insensitive even to major changes in the algorithm, and we also investigated calibration, where reported.

Differences between prognostic tests are best determined by both discrimination and calibration.

The AUC data provided by the studies were plotted in a graph by outcome and sex using Microsoft Excel for each tool examined. The review team then compared the AUCs across studies and produced narrative summaries, looking at inconsistency between studies. Data other than AUC (for example, sensitivity and specificity for certain thresholds, R2, D statistics and Brier scores) were also presented if given.

Calibration data were not often reported in the studies; calibration was either visually reported on a graph (observed risk versus 10-year predicted CVD risk) or values of the ratio of observed to predicted events were given.

3.3.7 Appraising the quality of the evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies was evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the evidence quality for each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables') which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of the intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent (using funnel plots for more than 4 studies).

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 3.3.8 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias ('Study Limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.

Quality element	Description
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.8 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High and observational studies as Low, uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated at 1 or2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections.

3.3.9 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over-or underestimation of true effect.

The risks of bias for intervention studies are listed in Table 5.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in randomised trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patients, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster randomised trials

3.3.10 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in the underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C). Pre-specified groups were defined for the majority of questions based on population. The review question on efficacy of statin therapy included the following additional groups: intensity of statin therapy, specific drug and dose, length of follow-up, baseline LDL-cholesterol level, placebo LDL-cholesterol level at follow-up and mean LDL-cholesterol reduction.

When heterogeneity existed (chi-square $p<0.1$ or I-squared inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation could be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty in the evidence contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.3.11 Indirectness

Directness relates to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Only populations defined in advance as strata were examined.

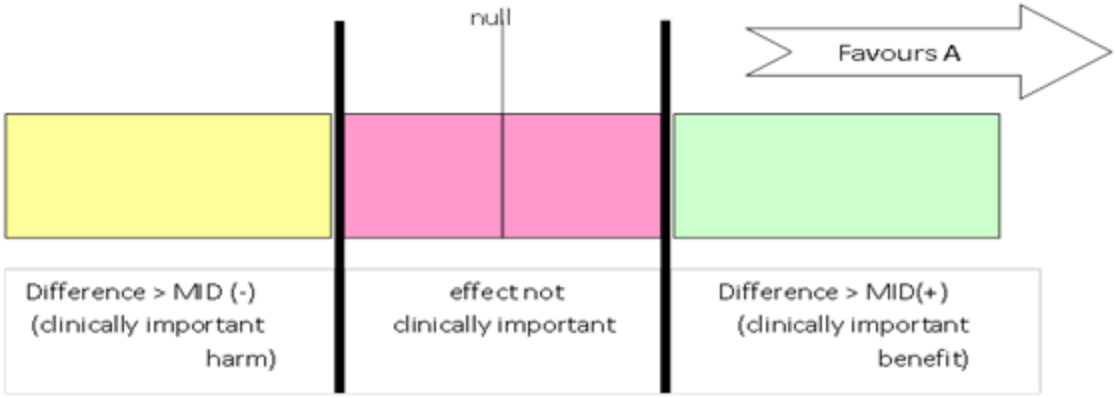
3.3.12 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead we are concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the confidence interval and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



Abbreviation: MID; minimal important difference

When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any acceptable MIDs for the outcomes in this guideline, but they confirmed the absence of research in the area. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important threshold for a risk ratio of 0.75 or 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews.

3.3.13 Quality assessment of risk assessment tools

The review on risk assessment tools compares different prognostic models (prediction tools) for predicting CVD risk on the basis of a combination of prognostic factors such as age, cholesterol level and smoking. The predictive tool incorporates all important risk factors and predicts absolute risks, which are compared with observed risks in validation studies. This is different to prognostic factor reviews (which are addressed by the Hayen checklist), in which the impact on outcomes of the presence versus the absence of a prognostic factor is compared. The risk prediction tool is closer to diagnostic studies and QUADAS-2. The new risk prediction tool checklist, PROBAST, has been developed for prognostic models of this type and is based on QUADAS-2: we used an adapted version of QUADAS-2 following advice from the GDG and the co-opted expert advisor on risk assessment tools. In prediction tools, risk of bias addresses the extent to which reported estimates of the predictive performance and accuracy (for example, coefficients, discrimination, calibration and re-classification estimates) are potentially biased, and applicability refers to the extent to which the reported prediction model matches the review question.

QUADAS-2 is a tool for the quality assessment of diagnostic accuracy studies.[276] The tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed on risk of bias and concerns about applicability. Where more than 1 test is compared within a study, there is an additional domain for multiple index tests. A rating is given for each domain and an overall risk of bias is then generated for each study. Applicability was assessed to decide whether the study population had direct or indirect applicability (appropriate for the review question or inappropriate as the population was very different from the UK), whether the risk stratification tool was directly applicable and whether the outcome (CVD events) was recorded or measured appropriately. QUADAS-2 was adapted for quality assessment of risk assessment tools. Adaptation was necessary to take into account the time dependence of prognosis, including the play of chance (that is, the fact that the event is yet to happen when we measure risk).

The following items were added to QUADAS-2 to capture some of the elements in prognostic studies and make the tool more relevant to prognostic evidence review:

- validation method (internal or external validation)
- imputation and exclusions for the prognostic factors in the index test: level of imputation (above or below 50%) including the number of factors requiring imputation; level of exclusions, including the number of factors with exclusions; assumed diagnosis for 1 or more factors
- whether the analysis is based on incidence data or time-to-event data
- source of data: index test or reference standard; data from a clinical database or a cohort
- number of (CVD) events: event rate above or below 100.

The GDG considered length of follow-up (or interval between index tests and reference standard) to be less important when the number of CVD events included in the study was adequate, that is, more

than 100. Blinding of outcome assessors to the risk stratification tool was also considered less important.

3.3.14 Assessing clinical importance and relative importance of outcomes

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

The GDG assigned the importance of outcomes in a qualitative way based on values and preferences, and also with consideration of the outcomes examined in the original Lipid modification guideline CG67.[177] The GDG considered the following outcomes as critical: all-cause mortality, CVD mortality, non-fatal MI, stroke and quality of life. These outcomes were prioritised for decision-making. Important outcomes included the following: sudden cardiac death and TIA. Relevant outcomes included the following: adverse events, hospitalisation and adherence. CG67 based recommendations on evidence from all-cause mortality and CVD outcomes; therefore, LDL-cholesterol reduction was not examined. In this guideline LDL-cholesterol reduction was only evaluated in the statin efficacy chapter. The GDG decided that in this instance information of LDL reduction achieved by individual statins might be required to inform recommendations for high-intensity statins and targets.

3.3.15 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements for intervention studies are presented by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- a brief description of the population
- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

The evidence statements for prognostic studies reflect the key finding as well as the quality of the studies.

3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[190] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in the highest priority area.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual.[190]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

3.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The guidelines manual.[190] and the health economics review protocol in Appendix C).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[190] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity. [204]

Table 6: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[190]

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for

new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified the cost effectiveness of statin therapy as the highest priority area for original economic modelling, due to statins being the preferred first-line treatment, substantial changes in the costs of statins since the previous version of this guideline was published, and a lack of published evidence using current UK costs, leading to considerable uncertainty regarding which intensity of statin is preferable and the threshold of CV risk above which primary preventative treatment should be initiated.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[191]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by an external health economist.

Full methods for the cost-effectiveness analysis for statin therapy are described in Appendix L.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[187] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[187]

3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

3.5 Developing recommendations

Underpinning this section is the concept of the 'strength' of a recommendation (Schünemann et al. 2003). This takes into account the quality of the evidence but is conceptually different. Some

recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summary of clinical and economic evidence and quality (as presented in Chapters 5-16).
- Forest plots and summary ROC curves (Appendix I).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix L).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 3.5.1 below).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions(See chapter 9.3; Creating guideline recommendations in the NICE Guidelines Manual[190])The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 8 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual.[190] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Identifying and assessing cardiovascular disease (CVD) risk

- 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]**
- Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. **[2008, amended 2014]**
- Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. **[new 2014]**
- Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria[a]. These people are at increased risk of CVD. See recommendation 62 for advice on treatment with statins for people with chronic kidney disease. **[new 2014]**

Lipid modification therapy for the primary and secondary prevention of CVD

- Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride concentrations. A fasting sample is not needed. **[new 2014]**
- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]**
- Start statin treatment in people with CVD with atorvastatin 80 mg[b]. Use a lower dose of atorvastatin if any of the following apply:
  - potential drug interactions
  - high risk of adverse effects
  - patient preference. **[new 2014]**
- Measure total cholesterol, HDL cholesterol and non HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non HDL cholesterol. If a greater than 40% reduction in non HDL cholesterol is not achieved:
  - discuss adherence and timing of dose
  - optimise adherence to diet and lifestyle measures
  - consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. **[new 2014]**

[a] People on renal replacement therapy are outside the scope of this guideline.

[b] At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[This recommendation updates and replaces recommendation 1.10.2.7 from Type 1 diabetes (NICE clinical guideline 15).]

4.2 Full list of recommendations

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]
2. Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008]
3. People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis. [2008]
4. Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]
5. Discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment. [2008]
6. Do not use opportunistic assessment as the main strategy in primary care to identify CVD risk in unselected people. [2008]
7. Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement. [2008]
8. Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]
9. Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes. See recommendations 59, 60 and 61 for advice on treatment with statins for people with type 1 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.1.2 from Type 1 diabetes (NICE clinical guideline 15).]
10. Use the QRISK2 risk assessment tool to assess CVD risk in people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendations 1.9.1 – 1.9.3 from Type 2 diabetes (NICE clinical guideline 87).]
11. Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria. These people are at increased risk of CVD. See recommendation 62 for advice on treatment with statins for people with chronic kidney disease. [new 2014]
12. Complete as many fields of the risk assessment tool as possible. [new 2014]
13. Routinely record ethnicity, body mass index and family history of premature CVD in medical records. [2008]
14. Consider socioeconomic status as an additional factor that contributes to CVD risk. [2008]
15. Do not use a risk assessment tool for people with pre-existing CVD. [2008, amended 2014]
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]

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]
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]
19. Recognise that CVD risk will be 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]
20. Severe obesity (body mass index greater than 40 kg/m^2) increases CVD risk. Take this into account when using risk scores to inform treatment decisions in this group (see Obesity [NICE clinical guideline 43]). [2008]
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]
22. NICE has produced guidance on the components of good patient experience in adult NHS services. These include recommendations on the communication of risk. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138). [new 2014]
23. Use everyday, jargon-free, language to communicate information on risk. If technical terms are used, explain them clearly. [2008]
24. Set aside adequate time during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required. [2008]
25. Document the discussion relating to the consultation on risk assessment and the person's decision. [2008]
26. Offer people 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:
    - presents individualised risk and benefit scenarios and
    - presents the absolute risk of events numerically and
    - uses appropriate diagrams and text. [2008]

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)
    - 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]
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]
29. Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturaed fats are replaced by mono-unsaturated and polyunsaturated fats. Further information and advice can be found at NHS Choices. [new 2014]
30. Advise people at high risk of or with CVD to:
    - reduce their saturated fat intake.
    - increase their mono-unsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils and to use them in food preparation.

    Further information and advice on healthy cooking methods can be found at NHS Choices. [new 2014]
31. Advise people at high risk of or with CVD to do all of the following:
    - choose wholegrain varieties of starchy food
    - reduce their intake of sugar and food products containing refined sugars including fructose
    - eat at least 5 portions of fruit and vegetables per day
    - eat at least 2 portions of fish per week, including a portion of oily fish
    - eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week.

    Further information and advice can be found at NHS Choices. [new 2014]
32. Advise pregnant women to limit their oily fish to no more than 2 portions per week and to avoid marlin, shark and swordfish. Further information and advice on oily fish consumption can be found at NHS Choices. [new 2014]

33. Take account of a person's individual circumstances – for example, drug therapy, comorbidities and other lifestyle modifications when giving dietary advice. [new 2014]

34. Advise and support people at high risk of or with CVD to achieve a healthy diet in line with Behaviour change: the principles for effective interventions (NICE public health guidance 6). [new 2014]

35. 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]

36. Advise people to do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). [new 2014]

37. 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]

38. Advice about physical activity should take into account the person's needs, preferences and circumstances. Agree goals and provide the person with written information about the benefits of activity and local opportunities to be active, in line with Four commonly used methods to increase physical activity (NICE public health guidance 2). [2008]

39. Give advice on diet and physical activity in line with national recommendations (see NHS Choices). [2008]

40. Offer people at high risk of or with CVD who are overweight or obese appropriate advice and support to work towards achieving and maintaining a healthy weight, in line with Obesity (NICE clinical guideline 43). [2008]

41. Be aware that men should not regularly drink more than 3–4 units a day and women should not regularly drink more than 2–3 units a day. People should avoid binge drinking. Further information can be found at NHS Choices. [2008]

42. Advise all people who smoke to stop, in line with Smoking cessation services (NICE public health guidance 10). [2008]

43. Offer people who want to stop smoking support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services). [2008]

44. If a person is unable or unwilling to accept a referral to an intensive support service, offer them pharmacotherapy in line with Smoking cessation services (NICE public health guidance 10) and Varenicline for smoking cessation (NICE technology appraisal guidance 123). [2008]

45. Do not advise any of the following to take plant stanols or sterols for the prevention of CVD:

    - people who are being treated for primary prevention

- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes
- people with type 2 diabetes. [new 2014]

46. Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. [2008]

47. When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost. [new 2014]

48. The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. [new 2014]

49. Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia. Include all of the following in the assessment:

    - smoking status
    - alcohol consumption
    - blood pressure (see Hypertension [NICE clinical guideline 127])
    - body mass index or other measure of obesity (see Obesity [NICE clinical guideline 43])
    - total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides
    - HbA_{1c}
    - renal function and eGFR
    - transaminase level (alanine aminotransferase or aspartate aminotransferase)
    - thyroid-stimulating hormone. [new 2014]

Primary prevention

50. Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. [new 2014]

51. Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes. (See Behaviour change: individual approaches [NICE public health guidance 49].) [new 2014]

52. Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. [new 2014]

53. If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. [new 2014]

54. Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]

55. For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48). [new 2014]

Secondary prevention

56. Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if any of the following apply:
    - potential drug interactions
    - high risk of adverse effects
    - patient preference. [new 2014]

57. Do not delay statin treatment in secondary prevention to manage modifiable risk factors. [2014]

58. 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]

People with Type 1 diabetes [Recommendations in this section [59-61] update and replace recommendations 1.10.1.3, 1.10.1.4, 1.10.1.5 and 1.10.2.4 from Type 1 diabetes (NICE clinical guideline 15)]

59. Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. [new 2014]

60. Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who:
    - are older than 40 years or
    - have had diabetes for more than 10 years or
    - have established nephropathy or
    - have other CVD risk factors. [new 2014]

61. Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]

People with Type 2 diabetes

62. Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014] [This recommendation updates and replaces recommendations 1.10.1.2, 1.10.1.3, and 1.10.1.5 from Type 2 diabetes (NICE clinical guideline 87).]

People with CKD

63. Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD.
    - Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 64) and eGFR is 30 ml/min/1.73 m^2 or more.
    - Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. [new 2014]

64. Measure total cholesterol, HDL cholesterol and non HDL cholesterol in all people who have been started on high-intensity statin treatment (both

primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non HDL cholesterol. If a greater than 40% reduction in non HDL cholesterol is not achieved:

- discuss adherence and timing of dose
- optimise adherence to diet and lifestyle measures
- consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014] [This recommendation updates and replaces recommendation 1.10.2.7 from Type 1 diabetes (NICE clinical guideline 15).]

65. If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. [new 2014]

66. Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group. [new 2014]

67. Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral. [new 2014]

68. Provide annual medication reviews for people taking statins.

- Use these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors.
- Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. [new 2014]

69. Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. [new 2014]

70. Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. [2008]

71. Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. [new 2014]

72. Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. [new 2014]

73. Exclude possible common secondary causes of dyslipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. [new 2014]

74. Consider the possibility of familial hypercholesterolaemia and investigate as described in Familial hypercholesterolaemia (NICE clinical guideline 71) if they have:
    - a total cholesterol concentration more than 7.5 mmol/litre and
    - a family history of premature coronary heart disease. [new 2014]
75. Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease. [new 2014]
76. Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control. [new 2014]
77. In people with a triglyceride concentration between 10 and 20 mmol/litre:
    - repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and
    - review for potential secondary causes of hyperlipidaemia and
    - seek specialist advice if the triglyceride concentration remains above 10 mmol/litre. [new 2014]
78. In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre:
    - be aware that the CVD risk may be underestimated by risk assessment tools and
    - optimise the management of other CVD risk factors present and
    - seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. [new 2014]
79. Do not offer coenzyme Q_{10} or vitamin D to increase adherence to statin treatment. [new 2014]
80. Advise people who are being treated with a statin:
    - that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins and
    - to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements. [new 2014]
81. Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses. [new 2014]
82. Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.
    - If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment.
    - If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose. [new 2014]

83. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase. [2008]

84. If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than 3 months. [new 2014]

85. Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. [2008]

86. Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin. Measure liver transaminase within 3 months of starting treatment and at 12 months, but not again unless clinically indicated. [2008]

87. Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal. [2008]

88. Do not stop statins because of an increase in blood glucose level or HbA_{1c}. (See the recommendations on assessing for risk of diabetes mellitus in Preventing type 2 diabetes [NICE public health guidance 38].) [new 2014]

89. Statins are contraindicated in pregnancy:

    - Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility.
    - Advise women planning pregnancy to stop taking statins 3 months before they attempt to conceive and to not restart them until breastfeeding is finished. [new 2014] [This recommendation updates and replaces recommendation 1.10.1.7 from Type 2 diabetes (NICE clinical guideline 87).]

90. Do not routinely offer fibrates for the prevention of CVD to any of the following:

    - people who are being treated for primary prevention
    - people who are being treated for secondary prevention
    - people with CKD
    - people with type 1 diabetes
    - people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendations 1.10.2.3 and 1.10.2.4 from Type 2 diabetes (NICE clinical guideline 87) and recommendations 1.10.2.5 and 1.10.2.6 from Type 1 diabetes (NICE clinical guideline 15).]

91. Do not offer nicotinic acid (niacin) for the prevention of CVD to any of the following:

    - people who are being treated for primary prevention
    - people who are being treated for secondary prevention
    - people with CKD
    - people with type 1 diabetes
    - people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.3.1 from Type 2 diabetes (NICE

clinical guideline 87) and recommendation 1.10.2.5 from Type 1 diabetes (NICE clinical guideline 15).]

92. Do not offer a bile acid sequestrant (anion exchange resin) for the prevention of CVD to any of the following:
    - people who are being treated for primary prevention
    - people who are being treated for secondary prevention
    - people with CKD
    - people with type 1 diabetes
    - people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.2.5 from Type 1 diabetes (NICE clinical guideline 15).]
93. Do not offer omega-3 fatty acid compounds for the prevention of CVD to any of the following:
    - people who are being treated for primary prevention
    - people who are being treated for secondary prevention
    - people with CKD
    - people with type 1 diabetes
    - people with type 2 diabetes. [new 2014]
94. Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. [new 2014]
95. Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. [new 2014]
96. People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal guidance 132). [2008][183]

July 2016 update: Recommendation 30 was amended to clarify the advice on saturated andmonounsaturated fat.

4.3 Key research recommendations

1. What is the effectiveness of age alone and other routinely available risk factors compared with the formal structured multi-factorial risk assessment to identify people at high risk of developing CVD?
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?
3. What is the effectiveness of statin therapy in older people?
4. What is the effectiveness of statin and/or other LDL cholesterol lowering treatment in people with type 1 diabetes?
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 people without established CVD?

4.4 How this clinical guideline was updated

The following sections of this guideline (2014) fully replace the reviews of CG67 (2008):

- 6 Full formal risk assessment of CVD risk
- 8 Cardioprotective diet
- 10 Plant stanols and sterols
- 11 Statins for the primary and secondary prevention of CVD
- 11.10 Adherence to statin therapy
- 11.11Advice and monitoring for adverse effects
- 12 Fibrates for the prevention of CVD
- 13 Nicotinic acid for the prevention of CVD
- 14 Bile acid sequestrants (anion exchange resins) for the prevention of CVD
- 15 Omega-3 fatty acid compounds for the prevention of CVD

The following sections of CH67 (2008) have not been update and the recommendations still apply:

- 5 Identification of people requiring assessment of CVD risk [2008]
- 7 Communication about risk assessment and treatment [2008]
- 9 Lifestyle modifications for the primary and secondary prevention of CVD [2008]
- 16 Ezetimibe [2008]

Please see Appendix O for details on the recommendations that have been updated and/or deleted from CG67 (2008).

5 Identification of people requiring assessment of CVD risk [2008]

5.1 Evidence statements for the identification of people at high risk of developing CVD

Economic modelling in an English primary care population showed that the most efficient strategy for identifying people at high risk of developing CVD is one which initially prioritises individuals based upon a prior estimate of their CVD risk using data already held in general practitioners' electronic medical records compared to using age or random assessment.

5.2 Clinical effectiveness of identification of people requiring assessment of CVD risk

In current clinical practice formal assessment of cardiovascular risk is done opportunistically. Entry into formal cardiovascular risk assessment is dependent on whether a person consults their general practitioner/general practice and or whether a risk factor such as high total cholesterol or high blood pressure is identified. This is also dependent on whether the clinician has the opportunity or makes the clinical decision to consider other issues in the consultation. This is therefore a two-stage process in which some initial choice is made over who receives a formal risk assessment. This has resulted in relatively low levels of both risk estimation and treatment of people at high risk of CVD and may also lead to treatment of people who are not at high risk by current criteria.[165,211,212]

2008

To improve primary prevention people at high risk must be identified and managed in the most efficient and coherent way. Half of men over 50 years and 20% of women over 65 years have a CVD risk of 20% or more. Within this group are people who have risks in excess of 30% or even 40%. A systematic approach to selection requires prior stratification of risk so that those at highest risk are reviewed first. This will result in a more effective choice of people for inclusion and a more efficient use of staff time and health service resources than an opportunistic approach.

This is not to say that people should never be assessed opportunistically outside of their rank order. Primary care will always involve random assessment initiated by either the patient or the clinician.

General practice records are now universally computerised and a high proportion of people have recording of smoking, blood pressure and, to a lesser extent, serum lipids. These records contain most of the information necessary to generate a prior estimate of cardiovascular risk based on existing data. Where data are missing they can be imputed on the basis of age- and sex-specific values drawn from population surveys.[155]

Using the recommended CVD risk equations, a prior estimate of CVD risk based on pre-existing information can be obtained and the practice population can be ranked from highest to lowest risk. Starting with those at highest risk, people can then be invited for a formal clinical assessment and risk factor estimation based on the measurement of blood pressure, lipids and current smoking status and taking account of other relevant factors such as family history, ethnicity and social or clinical circumstance.

Update 2014

The Department of Health instituted the NHS Health Check programme from April 2009. This programme invites all people between ages of 40 and 74 years for a health check which includes a CV risk assessment. Practices were able to implement the NHS Health Check programme in ways that suit the population of their area or practice and this may include the use of a prior estimate as described in the 2008 guideline. Following NHS re-organisation in April 2013, the programme is now the responsibility of local authorities, which work with general practices and commissioning groups to identify patients and invite them to their local practice, a pharmacy, or another designated provider for assessment. Strategies to prioritise people for assessment are not part of this guideline update. Some amendments have been made to the recommendations to bring them in line with the updated evidence reviews on risk tools and statins.

5.3 Cost-effectiveness identification of people requiring assessment of CVD risk [2008]

2008

See appendix C of the original CG67 guideline for the health economic models for the Lipid modification guideline CG67 (2008).

There were no full economic evaluation studies found discussing the identification strategies of patients eligible for CVD prevention in a primary care population. Marshall and Rouse modelled the costs and outcomes of a series of strategies for identification of patients eligible for CVD prevention in a primary care population.[157] The GDG requested Marshall's work be updated. The update included a Markov model estimating QALY gain from lifetime treatment with statins and the costs in different age bands and CVD risk bands. We used data derived from the Health Survey for England 2003 which consisted of 4264 individuals aged 30 to 74, free from CVD and without diabetes.

Various strategies were considered for identification of patients, the main comparisons being made between:

- Random assessment whereby patients are assessed in random order.
- Prioritisation by age whereby older individuals are assessed first.
- Prioritisation by age those aged over 50 then over 40 years.
- Prioritisation by a prior estimate of CVD risk whereby ten-year CVD risk is calculated for every individual based on risk factor data held in their electronic medical records.

The cost effectiveness outcome was cost per QALY by decile for the different strategies. The most efficient strategy will allocate people to treatment earlier, thus they will benefit from the statins. It will also misclassify fewer people as needing treatment when they don't need it.

2008

If all 4264 patients were assessed, the model estimates that 652 individuals will be diagnosed as clinically eligible for treatment. Untreated, we would expect these individuals to suffer from 81 CVD events over the next ten years. We would expect the 652 individuals diagnosed as clinically eligible for treatment to include 14 (2% of the total) individuals at low risk of CVD (less than 10% ten-year CVD risk) who had been misclassified as eligible for treatment. The screening process will identify 1% of the population aged between 35-44 years as eligible while the majority 87% of the patients will be aged over 65.

The cost-effectiveness results showed that using prior CVD information is the most cost-effective method of identifying those at risk of developing heart disease. When all the relevant 12 strategies are compared, the analysis suggests that it's cost-effective to screen 20% of the relevant population. The ICER is about £7,604/QALY when prior CVD is compared with the next best non-dominated option (10% prior CVD). The ICER for 30% prior CVD compared with the next best non-dominated option (20% prior CVD) is about £37,644 per QALY.

5.4 Conclusions

Primary prevention of CVD should make use of strategies to prioritise patients likely to be at highest risk and to invite patients in descending order of CVD risk estimated from available data in the GP database. UK general practices have enough data to use this systematic way.

5.5 Recommendations [2008]

Recommendations	**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]** **2. Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008]** **3. People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis. [2008]** **4. Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]** **5. Discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment. [2008]** **6. Do not use opportunistic assessment as the main strategy in primary care to identify CVD risk in unselected people. [2008]** **7. Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement. [2008]**

2008

6 Full formal risk assessment of CVD risk

6.1 Introduction

The process of atherosclerosis that leads to CVD is difficult to diagnose easily, prior to the occurrence of significant clinical events such as CVD-related death, myocardial infarction or stroke. Epidemiological studies, such as the Framingham cohort studies in the USA, have identified a large number of CVD risk factors which can be divided into the principal non-modifiable CVD risk factors, such as age and gender, and modifiable risk factors, including smoking, blood pressure, presence of diabetes and ratio of total cholesterol to HDL cholesterol. The significance of these principal risk factors has been confirmed in worldwide epidemiological cohort studies, including in the UK. The cohort studies can be used to devise risk tools that calculate the percentage risk of a CVD event prospectively over a defined period of time, for example a decade. While the basic set of CVD risk factors is well established, numerous groups have proposed the addition of other CVD risk factors, such as obesity, ethnicity, family history of premature CVD or markers of inflammation, to improve the performance of the risk tools, particularly in subgroups.

The previous NICE guideline on lipid modification and CVD risk assessment (CG67) recommended the use of a risk assessment tool derived from the US Framingham and Framingham Offspring studies to assess CVD risk. Multiple different risk assessment tools have been derived from the Framingham study[238,238] and the Anderson (1991) tool was chosen.[17,17] The GDG suggested a number of adjustments to the equation to improve estimation of risk, particularly in people from minority ethnic groups**.** During the validation phase of the guideline, the first paper describing the development and internal validation of QRISK was published and the guideline group considered it alongside Framingham. QRISK was derived from patient records in a large UK primary care database. The GDG view was that it was premature at that time to recommend QRISK. A summary GDG discussion is summarised in Appendix Q. Following publication of further literature validating QRISK, NICE withdrew advice about which risk assessment tool to use in February 2010. In this update, the GDG were asked to consider whether they could recommend one tool for assessment of CVD risk.

Risk assessment of CVD has relevance for the use of lipid modification drugs, but is also relevant to the NICE Hypertension guideline (CG127) which cross-refers to this guideline and recommends treatment for mild hypertension on the basis of overall CVD risk. The scope for this guideline includes populations with type 1 and type 2 diabetes and people with CKD. The scope also includes consideration of risk assessment in 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 and people with serious mental illness.

The GDG requested that information on age alone as an indicator of risk be reported alongside the review on risk tools. Age is the principal determinant of risk and has the potential to be a simple way of considering who might benefit from preventative treatment.

6.2 Clinical evidence

We have only included tools which have been validated in England and Wales (QRISK2, Framingham and UKPDS). Data on age alone were also extracted where available.

QRISK2 (http://www.qrisk.org/) and Framingham (http://cvdrisk.nhlbi.nih.gov/calculator.asp) are 2 online risk assessment tools for estimating the 10-year risk of having a CV event, for people who do not already have heart disease. The definition of CVD is slightly different in the 2 tools. In the Framingham tool, CVD comprises coronary death, MI, coronary insufficiency, angina, ischemic stroke, haemorrhagic stroke, TIA, PAD, and heart failure. In the QRISK2 tool, CVD comprises CHD (angina and MI), stroke, and TIA, but not PAD). QRISK2 is available as lifetime CV risk calculator

(http://qrisk.org/lifetime/); Framingham has also been developed as lifetime CV risk calculator, however, it is not publicly available.

UKPDS Risk Engine (http://www.dtu.ox.ac.uk/riskengine/) is a type 2 diabetes-specific risk calculator for estimating the 10-year risk of CHD (fatal and non-fatal MI, and sudden cardiac death) and stroke (both fatal and non-fatal).

The risk factors and variables included in the tools (10-year risk) are listed in Table 7.

Table 7: Risk factors and variables included in the risk assessment tools

Risk factors/variables	QRISK2	Framingham	UKPDS	Age alone
Self-assigned ethnicity	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed	–	Caucasian or Asian-Indian/ Afro-Caribbean in the CHD tool. Ethnicity not significant in the stroke tool.	–
Age	Years	Years	Years	Years
Sex	Male/Female	Male/Female	Male/Female	–
Smoking status	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)	Yes/No	Current smoker, non-smoker (including ex-smoker)	–
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)	Continuous (mmHg)	–
Total serum cholesterol and high density lipoprotein cholesterol	Ratio of total to HDL-C; continuous	Total and HDL- C entered separately; continuous (mg/dl)	Total and HDL- C entered separately; continuous (mmol/litre) The model equation uses the ratio of total to HDL-C	–
Body mass index (BMI)	Continuous	–	–	–
Family history of coronary heart disease in first degree relative under 60 years	Yes/No	–	–	–
Townsend deprivation score (output area level 2001 census data evaluated as a continuous variable)	Postcode	–	–	–
Treated hypertension	Yes/No	Yes/No	–	–
Rheumatoid arthritis	Yes/No	–	–	–
Chronic kidney disease	Yes/No	–	–	–

Risk factors/variables	QRISK2	Framingham	UKPDS	Age alone
Atrial fibrillation	Yes/No	–	Yes/No (not included in the CHD tool)	–
Type 1 diabetes	Yes/No	–	–	–
Type 2 diabetes	Yes/No	–	HbA_{1c} (%)(but not significant in the stroke calculator)	–
Duration of diabetes	–	–	Years	–

Twenty-four studies were included in the review.[18,36,38,48,52,54,56,83,108,115,116,129,134,161,215,216,240-242,253,254,266,267,279] Evidence from these are summarised in the paragraphs below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

6.2.1 Summary of included studies

Table 8: Summary of studies included in the review

	Summary of study					QUADAS II quality assessment	
Author, Year (cohort)	Risk tools	Country	Age, years (range)	Population (n)	CVD/ CHD events (n)	Overall risk of bias	Applicability
Hippisley-Cox 2008[116] (QRESEARCH) Development and validation of QRISK2 (10-year risk)	- QRISK2-2008 - Modified NICE Framingham	UK	35–74	2,285,815	96,709 CVD	High	Direct
Hippisley-Cox 2010[115] (QRESEARCH) Development and validation of QRISK2 (lifetime risk)	- QRISK2-2011	UK	30–84	3,601,918	121,623 CVD	High	Direct
Collins 2012B[54,55] (THIN) External validation of QRISK2	- QRISK2-2011 - Modified NICE Framingham	UK	30–84	2,084,445	93,563 CVD	High	Direct
Anderson 1991[17,18] (Framingham and Framingham offspring cohorts) Development of Framingham-Anderson	Framingham-Anderson	USA	30–74	2590	1252 CHD	Unclear	Indirect
Brindle 2003[36,36] (British regional	Framingham-Anderson	UK	40–59	6643	677 CHD	High	Direct

	Summary of study					QUADAS II quality assessment	
Author, Year (cohort)	**Risk tools**	**Country**	**Age, years (range)**	**Population (n)**	**CVD/ CHD events (n)**	**Overall risk of bias**	**Applicability**
heart study) Validation of Framingham-Anderson							
Ramachandran 2000[215,215]	Framingham-Anderson	UK	30–75	1700	529 CHD	Very high	Direct
Wannamethee 2005[267,267]	Framingham-Anderson	UK	30–75	5128	1060 CHD	Low	Direct
Cooper 2005[56,56]	Framingham-Anderson	UK	50–64	2732	219 CHD	High	Direct
Ramsay 2011[216,216]	Framingham-Anderson	UK	40–59	6467	647 CHD	Low	Direct
May 2006[161,161]	Framingham-Anderson	UK	60–79	3853	198 CHD 240 CVD	High	Direct
Wilson 1998[279,279] (Framingham and Framingham offspring cohorts) Development of Framingham-Wilson	Framingham-Wilson	USA	30–74	5345	610 CHD	Unclear	Indirect
Simmons 2008[242,242]	Framingham-Wilson	UK	40–79	10,295	680 CHD	Low	Direct
Brunner 2010[38,38]	Framingham-Wilson	UK	40–63	6868	443 CHD	Low	Direct
Chamnan 2010[47,48]	Framingham-D'Agostino	UK	40–74	21,867	2213 CVD	Low	Direct
Jones 2001[97,97]	Framingham-Wilson	UK	30–70	691	CHD (number not reported)	High	Direct
Simmonds 2012[240,240]	- QRISK2 - Framingham-Anderson	UK	40–74	500,000	CVD (number not reported)	Very high	Direct
Wald 2011[266,266]	- Age alone - Framingham-Anderson	UK	0–89	500,000	465 CVD per 10,000 patients	Very high	Direct
Studies in diabetic population (type 2 diabetes)							
Stevens 2001[254,254] (Development of UKPDS, CHD events)	UKPDS	UK	25–65	4540	CHD (number not reported)	Low	Direct
Kothari	UKPDS	UK	25–65	4540	Stroke	Low	Direct

	Summary of study					QUADAS II quality assessment	
Author, Year (cohort)	**Risk tools**	**Country**	**Age, years (range)**	**Population (n)**	**CVD/ CHD events (n)**	**Overall risk of bias**	**Applicability**
2002[134,134] (Development of UKPDS, stroke)					(188)		
Stephens 2004[253,253]	UKPDS	UK	35–74	798	358 CVD 269 CHD	Low	Direct
Guzder 2005[108,108]	- UKPDS - Framingham-Anderson	UK	30–74	428	98 CVD 60 CHD	High	Direct
Elkeles 2008[82,83]	- UKPDS - Framingham-Anderson	UK	50–75	589	66 CVD 56 CHD	High	Direct
Simmons 2009[241,242]	- UKPDS - Framingham-D'Agostinio	UK	40–79	10,137	961 CVD	Low	Direct
Coleman 2007[52,52] (Framingham-applied to the UKPDS cohort)	Framingham-Anderson	UK	25–65	3898	288 CVD 246 CHD	Unclear	Direct

6.2.2 Summary of results

Table 9: Summary of results: AUC

Tool and outcome	Subgroup	AUC (95% CI)
Hippisley-Cox 2008.[116] Head-to-head comparison QRISK2 versus NICE Framingham; QRESEARCH database		
QRISK2. CVD	Women	0.817 (0.814–0.820)
QRISK2. CVD	Men	0.792 (0.789–0.794)
NICE Framingham. CVD	Women	0.800 (0.797–0.803)
NICE Framingham. CVD	Men	0.779 (0.776–0.782)
Collins 2012.[54,55] Head-to-head comparison QRISK2 versus NICE Framingham; THIN database		
QRISK2-2011. CVD	Women aged 30–84	0.835 (0.834–0.837)
QRISK2-2010. CVD	Women aged 30–84	0.835 (0.833–0.837)
QRISK2-2011. CVD	Men aged 30–84	0.809 (0.807–0.811)
QRISK2-2010. CVD	Men aged 30–84	0.811 (0.809–0.812)
QRISK2-2011. CVD	Women aged 35–74	0.802 (0.800–0.804)

Tool and outcome	Subgroup	AUC (95% CI)
QRISK2-2008. CVD	Women aged 35–74	0.800 (0.798–0.803)
QRISK2-2011. CVD	Men aged 35–74	0.771 (0.769–0.773)
QRISK2-2008. CVD	Men aged 35–74	0.772 (0.769–0.774)
NICE Framingham. CVD	Women aged 35–74	0.776 (0.773–0.779)
NICE Framingham. CVD	Men aged 35–74	0.750 (0.747–0.752)
Hippisley-Cox 2010.[115] Lifetime QRISK2; QRESEARCH database		
QRISK2. CVD	Women	0.842 (0.840–0.844)
QRISK2. CVD	Men	0.828 (0.826–0.830)
Wannamethee 2005.[267,267] British Regional Heart Study		
Framingham-Anderson. CHD	Men	0.73 (0.71–0.75)
Cooper 2005.[56,56] Second Northwick Park Heart Study (NPHS-II)		
Framingham-Anderson. CHD	Men	0.62 (0.58–0.66)
May 2006.[161,161] British Women's Heart and Health Study		
Framingham-Anderson. CHD	Women	0.59 (0.56–0.63)
Framingham-Anderson. CVD	Women	0.62 (0.58–0.65)
Wilson 1998.[279,279] Framingham and Framingham Offspring cohorts. Development of sex-specific algorithms.		
Framingham-Wilson. CHD	AUC associated with T-C categories, continuous variables, men	0.74
Framingham-Wilson. CHD	AUC associated with T-C categories, categorical variables, men	0.73
Framingham-Wilson. CHD	AUC associated with T-C categories, risk factor sum, men	0.69
Framingham-Wilson. CHD	AUC associated with T-C categories, continuous variables, women	0.77
Framingham-Wilson. CHD	AUC associated with T-C categories, categorical variables, women	0.76
Framingham-Wilson. CHD	AUC associated with T-C categories, risk factor sum, women	0.72
Framingham-Wilson. CHD	AUC associated with LDL-C categories, continuous variables, men	0.74

Tool and outcome	Subgroup	AUC (95% CI)
Framingham-Wilson. CHD	AUC associated with LDL-C categories, categorical variables, men	0.73
Framingham-Wilson. CHD	AUC associated with LDL-C categories, risk factor sum, men	0.68
Framingham-Wilson. CHD	AUC associated with LDL-C categories, continuous variables, women	0.77
Framingham-Wilson. CHD	AUC associated with LDL-C categories, categorical variables, women	0.77
Framingham-Wilson. CHD	AUC associated with LDL-C categories, risk factor sum, women	0.71
Simmons 2008.[242,242] European Prospective Investigation of Cancer (EPIC) Norfolk.		
Framingham-Wilson. CHD	Men	0.71 (0.69–0.73)
Framingham-Wilson. CHD	Women	0.71 (0.38–0.74)
Brunner 2010.[38,38] Whitehall II study, from phase 3		
Framingham-Wilson. CHD		0.70 (0.68–0.73)
Chamnan 2010[47,48]		
Framingham-D'Agostino. CVD		0.77 (0.76–0.78)
Abbreviation: T-C; total cholesterol		

Table 10: Summary of results: AUC for the diabetes strata only

Tool and outcome	Subgroup	AUC (95% CI)
Guzder 2005.[108,108] Head-to-head comparison UKPDS versus Framingham. Poole Diabetes Study		
Framingham-Anderson. CVD	Type 2 diabetes	0.673 (0.612–0.734)
Framingham-Anderson. CHD	Type 2 diabetes	0.657 (0.581–0.732)
UKPDS. CHD	Type 2 diabetes	0.670 (0.598–0.742)
Elkeles 2008.[82,83] Head-to-head comparison UKPDS (version 3) **versus Framingham. PREDICT study**		
Framingham-Anderson. CHD	Type 2 diabetes	0.63 (0.55–0.71)
UKPDS. CHD	Type 2 diabetes	0.67 (0.60–0.75)
UKPDS. CVD	Type 2 diabetes	0.63 (0.56–0.71)
Simmons 2009.[241,242] Head-to-head comparison UKPDS (version 3) versus Framingham. EPIC-Norfolk Cohort		
Framingham-D'Agostino. CVD	Diabetes	0.73 (0.66–0.78)

Tool and outcome	Subgroup	AUC (95% CI)
UKPDS. CVD	Diabetes	0.72 (0.65–0.78)
Framingham-D'Agostino. CVD	Non-diabetic hyperglycaemia	0.66 (0.62–0.71)
UKPDS. CVD	Non-diabetic hyperglycaemia	0.68 (0.63–0.72)
Framingham-D'Agostino. CVD	Normo-glycaemic	0.77 (0.76–0.79)
UKPDS. CVD	Normo-glycaemic	0.77 (0.76–0.79)
Stephens 2004[253,253]		
UKPDS. CVD	Diabetes	0.74 (0.70–0.78)
UKPDS. CHD	Diabetes	0.76 (0.72–0.80)
Coleman 2007.[52,52] UKPDS cohort		
Framingham-Anderson. CVD	Type 2 diabetes	0.76

Note: QRISk2 includes type 1 and type 2 diabetes as risk factors, but there are not separate results for the diabetes population only.

Table 11: Summary of results: R^2, D statistics and Brier score

Tool and subgroup	R^2 (%)	D statistics	Brier Score
Hippisley-Cox 2008.[116] Head-to-head comparison QRISK2 versus NICE Framingham			
QRISK2 (women)	43.47 (42.78–44.16)	1.795 (1.769–1.820)	0.086 (0.083–0.089)
QRISK2 (men)	38.38 (37.75–39.01)	1.615 (1.594–1.637)	0.136 (0.134–0.139)
NICE Framingham (men)	38.87 (38.12–39.62)	1.632 (1.606–1.658)	0.093 (0.090–0.096)
NICE Framingham (men)	34.78 (34.12–35.45)	1.495 (1.473–1.517)	0.177 (0.174–0.180)
Collins 2012.[54,55] Head-to-head comparison QRISK2 versus NICE Framingham			
QRISK2-2011 (women aged 30–84)	48.3 (47.9–48.7)	1.98 (1.96–1.99)	NR
QRISK2-2010 (women aged 30–84)	48.1 (47.7–48.6)	1.97 (1.95–1.99)	NR
QRISK2-2011 (men aged 30–84)	41.6 (41.2–42.0)	1.73 (1.71–1.75)	NR
QRISK2-2010 (men aged 30–84)	42.5 (42.0–42.8)	1.76 (1.74–1.77)	NR
QRISK2-2011 (women aged 35–74)	40.1 (39.5–40.6)	1.67 (1.65–1.69)	NR
QRISK2-2008 (women aged 35–74)	39.5 (36.6–42.4)	1.66 (1.56–1.76)	NR
QRISK2-2011 (men aged 35–74)	33.1 (32.6–33.6)	1.44 (1.42–1.46)	NR
QRISK2-2008	33.3	1.45	NR

Tool and subgroup	R^2 (%)	D statistics	Brier Score
(men aged 35–74)	(28.9–37.8)	(1.31–1.59)	
NICE Framingham (women aged 35–74)	34.2 (33.6–34.9)	1.48 (1.46–1.50)	NR
NICE Framingham (men aged 35–74)	29.2 (28.7–29.7)	1.31 (1.30–1.33)	NR
Hippisley-Cox 2010.[115] Lifetime QRISK2			
QRISK2 (women)	47.0 (46.5–47.5)	NR	NR
QRISK2 (men)	43.4 (42.9–43.9)	NR	NR
Abbreviation: NR; not reported			

Table 12: Summary of results: ratio observed to predicted of CHD events or CVD events as stated

Tool and outcome	Subgroup	Ratio observed to predicted
Cooper 2005.[56,56] Second Northwick Park Heart Study (NPHS-II)		
Framingham-Anderson. CHD events.	Men	0.47
Ramsay 2011.[216,216] British Regional Heart Study (BRHS), according to social class.		
Framingham-Anderson. CHD events.	Men. Social class I (n=535)	2.39 (1.85–2.93)
Framingham-Anderson. CHD events.	Men. Social class II (n=1518)	1.87 (1.36–2.37)
Framingham-Anderson. CHD events.	Men. Social class III NM (n=632).	1.53 (1.05–2.01)
Framingham-Anderson. CHD events.	Men. Social class III M (n=2832)	1.55 (1.07–2.03)
Framingham-Anderson. CHD events.	Men. Social class IV (n=679)	1.42 (0.93–1.90)
Framingham-Anderson. CHD events.	Men. Social class V (n=271)	1.18 (0.70–1.66)
Framingham-Anderson. CHD events.	Men. Non-manual (n=2685)	1.84 (1.33–2.34)
Framingham-Anderson. CHD events.	Men. Manual (n=3782)	1.49 (1.01–1.97)
May 2006.[161,161] British Women's Heart and Health Study		
Framingham-Anderson. CHD events.	Women	1.03
Framingham-Anderson. CVD events.	Women	1.54
Chamnan 2010.[47,48] EPIC-Norfolk Study		
Framingham-D'Agostino. CVD events.	Men and women	1.60

Table 13: Summary of results: ratio predicted to observed of CHD events or CVD events as stated, in diabetic population

Tool and outcome	Subgroup	Ratio predicted to observed
Guzder 2005.[108,108] Head-to-head comparison UKPDS versus Framingham. Poole Diabetes Study		
Framingham-Anderson. CVD events.	Type 2 diabetes	0.67
Framingham-Anderson. CHD events.	Type 2 diabetes	0.68
UKPDS. CHD events.	Type 2 diabetes	0.87

Note: QRISk2 includes type 1 and type 2 diabetes as risk factors, but there are not separate results for the diabetes population only.

Table 14: Summary of results: sensitivity and specificity

Tool	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Threshold* or age cut-off
Brindle 2003[36,36]			
Framingham-Anderson	16	94	30%

Tool	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Threshold* or age cut-off
Framingham-Anderson	75	55	15%
Modified Framingham (score/1.47)	1.8	99.	30%
Modified Framingham (score/1.47)	37	85	15%
Wannamethee 2005.[267,267] British Regional Heart Study			
Framingham-Anderson	56.5	75.0	NR
Ramsay 2011.[216,216] British Regional Heart Study (BRHS), according to social class.			
Framingham-Anderson. Social class I (n=535)	53 (34–72)	85 (82–88)	20%
Framingham-Anderson. Social class II (n=1518)	56 (47–65)	79 (77–81)	20%
Framingham-Anderson. Social class III NM (n=632)	57 (45–69)	76 (72–79)	20%
Framingham-Anderson. Social class III M (n=2832)	54 (49–60)	73 (71–75)	20%
Framingham-Anderson. Social class IV (n=679)	47 (36–59)	74 (70–77)	20%
Framingham-Anderson. Social class V (n=271)	37 (22–54)	74 (68–79)	20%
Framingham-Anderson. Non-Manual (n=2685)	56 (49–63)	79 (78–81)	20%
Framingham-Anderson. Manual (n=3782)	52 (47–56)	73 (71–75)	20%
May 2006.[161,161] British Women's Heart and Health Study			
Framingham-Anderson. CHD events.	10	95	30%
Framingham-Anderson. CVD events	38	79	30%
Chamnan 2010.[47,48] EPIC-Norfolk Study			
Framingham-D'Agostino. CVD events	41.4 (39.4–43.5)	87.8 (87.3–88.3)	30%
Framingham-D'Agostino. CVD events	67.5 (63.7–67.7)	73.6 (73.0–74.2)	20%
Framingham-D'Agostino. CVD events	79.3 (77.5–81.0)	61.2 (60.5–61.8)	15%
Wald 2011.[266,266] Simulated population			
Framingham-Anderson	66	91	20%
Age alone	66	88	66 years
Framingham-Anderson	86	79	8%
Age alone	86	76	55 years
Framingham-Anderson	91	73	5%
Age alone	91	69	50 years
Simmonds 2012.[240,240] Simulated population			
Framingham-Anderson	79	80	15%
QRISK2	73	80	16 years

Tool	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Threshold* or age cut-off
Jones 2001[129,129]			
Framingham-Wilson	67.0 (53.7–77.3)	97.6 (96.0–98.7)	27%
Framingham-Wilson	82.4 (77.0–86.9)	93.9 (91.0–96.1)	15%

**Thresholds are either for CVD or CHD as reported by the studies (please refer to Table 8 for details).*

Table 15: Summary of results: sensitivity and specificity, in diabetic population

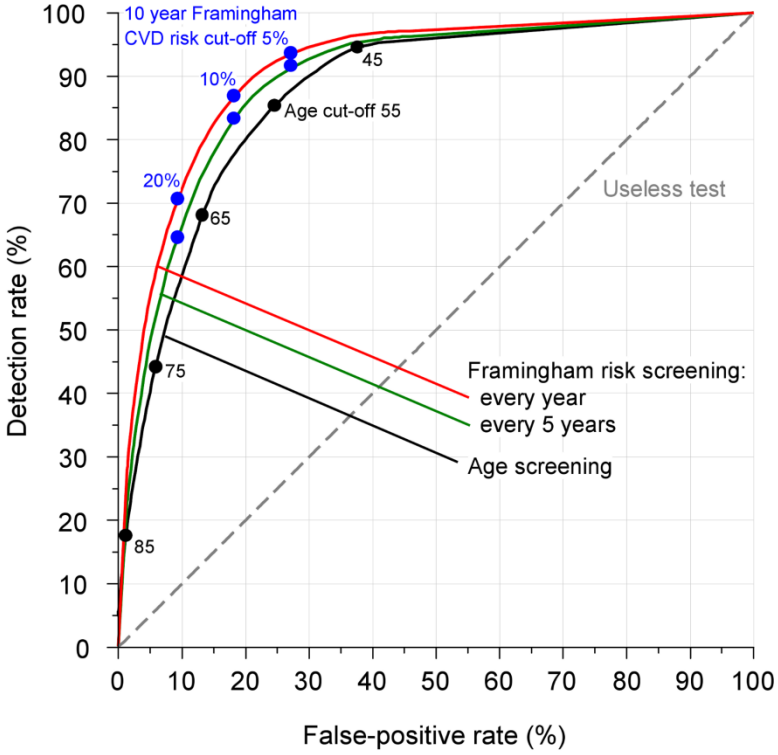
Tool	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Threshold
Guzder 2005.[108,108] Head-to-head comparison UKPDS versus Framingham. Poole Diabetes Study			
Framingham-Anderson	29.6 (22.2–37.2)	88.5 (86.3–90.7)	30% and T-C >5 mmol/l
UKPDS	50.0 (39.7–60.3)	69.1 (63.8–74.0)	30% and T-C >5 mmol/l
Framingham-Anderson	72.4 (63.5–80.2)	45.2 (42.5–47.5)	15% and T-C >5 mmol/l
UKPDS	76.5 (66.9–84.5)	46.4 (40.9–51.9)	15% and T-C >5 mmol/l
Framingham-Anderson	85.7 (77.8–91.5)	33.0 (30.7–34.7)	15% only
UKPDS	89.2 (82.0–95.0)	30.3 (25.4–35.6)	15% only
Simmons 2009.[241,242] Head-to-head comparison UKPDS versus Framingham. EPIC-Norfolk Cohort			
Framingham-D'Agostino (diabetes)	86	30	20%
UKPDS (diabetes)	94	31	20%
Framingham- D'Agostino (non-diabetic hyperglycaemia)	90	26	20%
UKPDS (non-diabetic hyperglycaemia)	94	22	20%
Framingham- D'Agostino (normo-glycaemic)	96	20	20%
UKPDS (normo-glycaemic)	97	15	20%
Abbreviation: T-C; total cholesterol			

Note: QRISk2 includes type 1 and type 2 diabetes as risk factors, but there are not separate results for the diabetes population only.

6.2.3 ROC curves

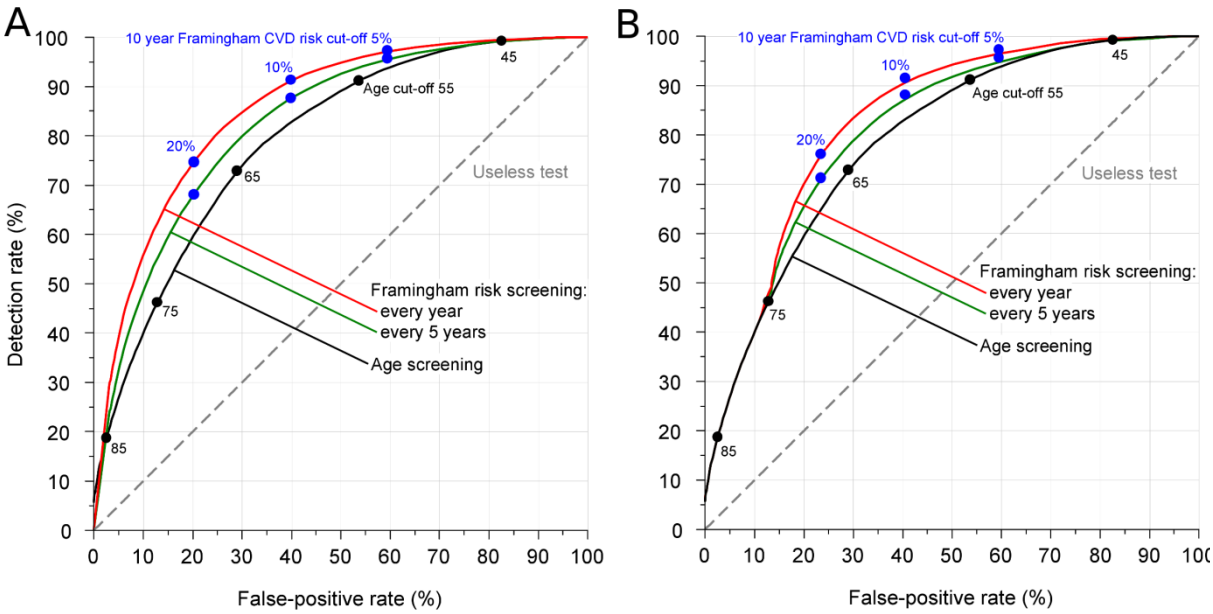
Figure 3 and Figure 4 (from Wald 2011[266,266]) show the ROC curves for age alone, Framingham every year and Framingham every 5 years, with selected ages and risk cut-offs. They are based on a simulated population of 500,000 individuals aged from 0 to 89 (the means and standard deviations of risk factors in 10-year age and sex groups are taken from the Health Survey for England). However, it would be desirable for the estimates to be independently validated against data from a cohort study.

Figure 3: Detection rate (sensitivity) against false-positive rate (100-specificity) for Framingham and age alone, showing selected age and Framingham risk cut-offs, performed in a simulated population study (From Wald 2011[266,266]).



Source: Wald NJ, Simmonds M, Morris JK (2011) [266,266] Screening for Future Cardiovascular Disease Using Age Alone Compared with Multiple Risk Factors and Age. PLoS ONE 6(5): e18742. doi:10.1371/journal.pone.0018742

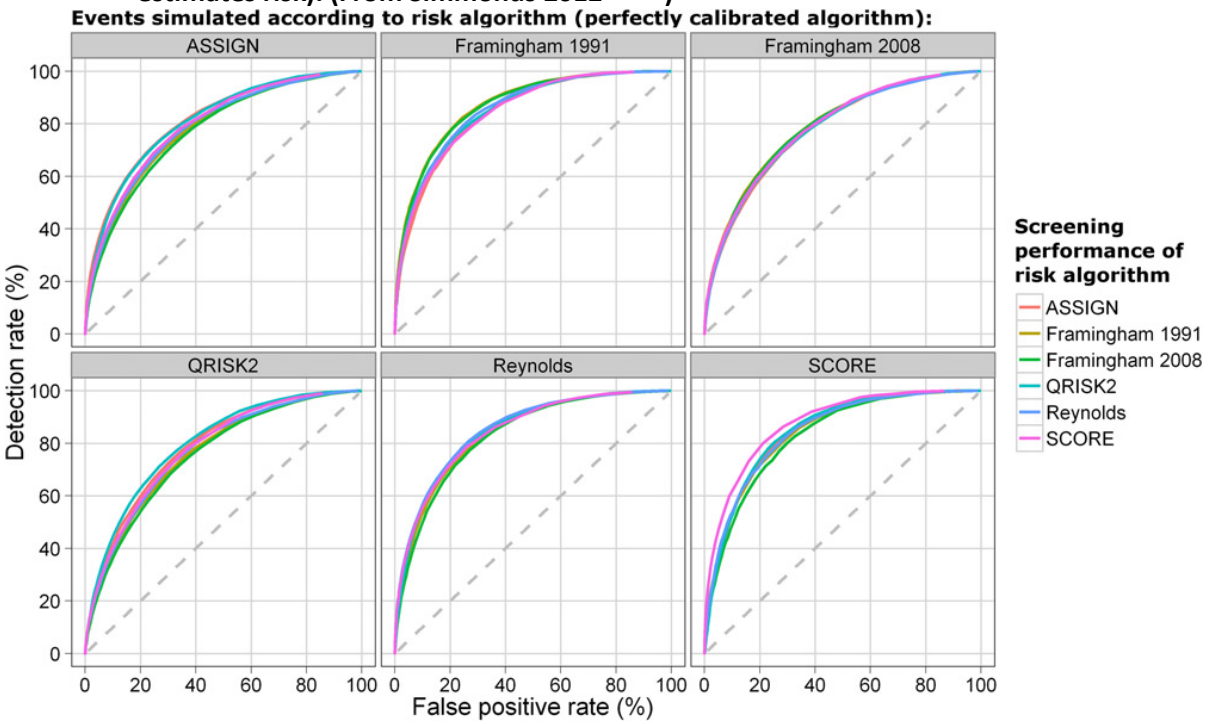
Figure 4: Detection rate (sensitivity) against false-positive rate (100-specificity) for Framingham and age alone: (a) in people aged 40–89; (b) Framingham to age 74, then treat everybody until age 89performed in a simulated population study (From Wald 2011[266,266])



Source: Wald NJ, Simmonds M, Morris JK (2011) [266,266] Screening for Future Cardiovascular Disease Using Age Alone Compared with Multiple Risk Factors and Age. PLoS ONE 6(5): e18742. doi:10.1371/journal.pone.0018742

Figure 5 (From Simmonds 2012[240,240]) shows 6 ROC curves, one sub-figure for each of the 6 CVD risk algorithms, according to which algorithms was used to simulate CVD events. They are based on a simulated population of 500,000 individuals aged from 40 to 75.

Figure 5: ROC curves for 6 CVD risk algorithms according to which algorithm was used to simulate CVD events in a simulated population study (that is, which algorithm perfectly estimates risk). (From Simmonds 2012[240,240])

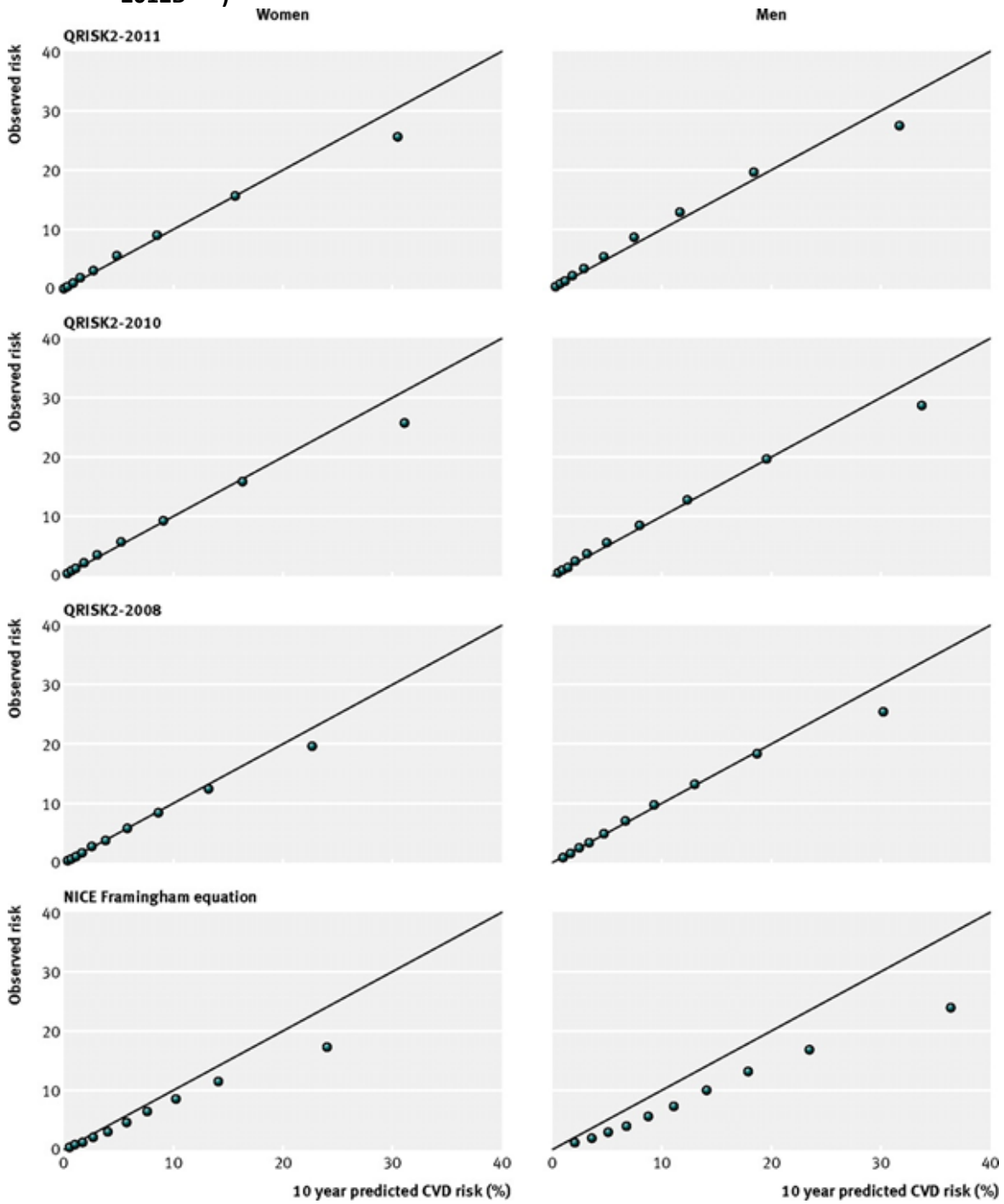


Source: Simmonds 2012[240,240]
J Med Screen 2012;19:201–205
DOI: 10.1258/jms.2012.012076

6.2.4 Calibration curves

Figure 6 (Collins 2012B[54,55]) shows the calibration plots for the 3 versions of QRISK2 and the NICE version of the Framingham equation. The current version of QRISK2 and its predecessors show better agreement between the observed risk and the predicted risk grouped by 10th of risk than does the NICE Framingham equation. All 3 versions of the QRISK2 prediction models show good calibration in all 10^{ths} of risk, with the exception of the highest 10th of risk in both men and women (calibration slope, range 0.92–0.95). The NICE Framingham equation is mis-calibrated, most noticeably for men, with a near constant over-prediction of about 5%.

Figure 6: Calibration curves: observed versus predicted 10-year risk of CVD (from Collins 2012B[54,55])



Source: from Collins 2012B[54,55]
BMJ 2010;340:c2442
doi:10.1136/bmj.c2442
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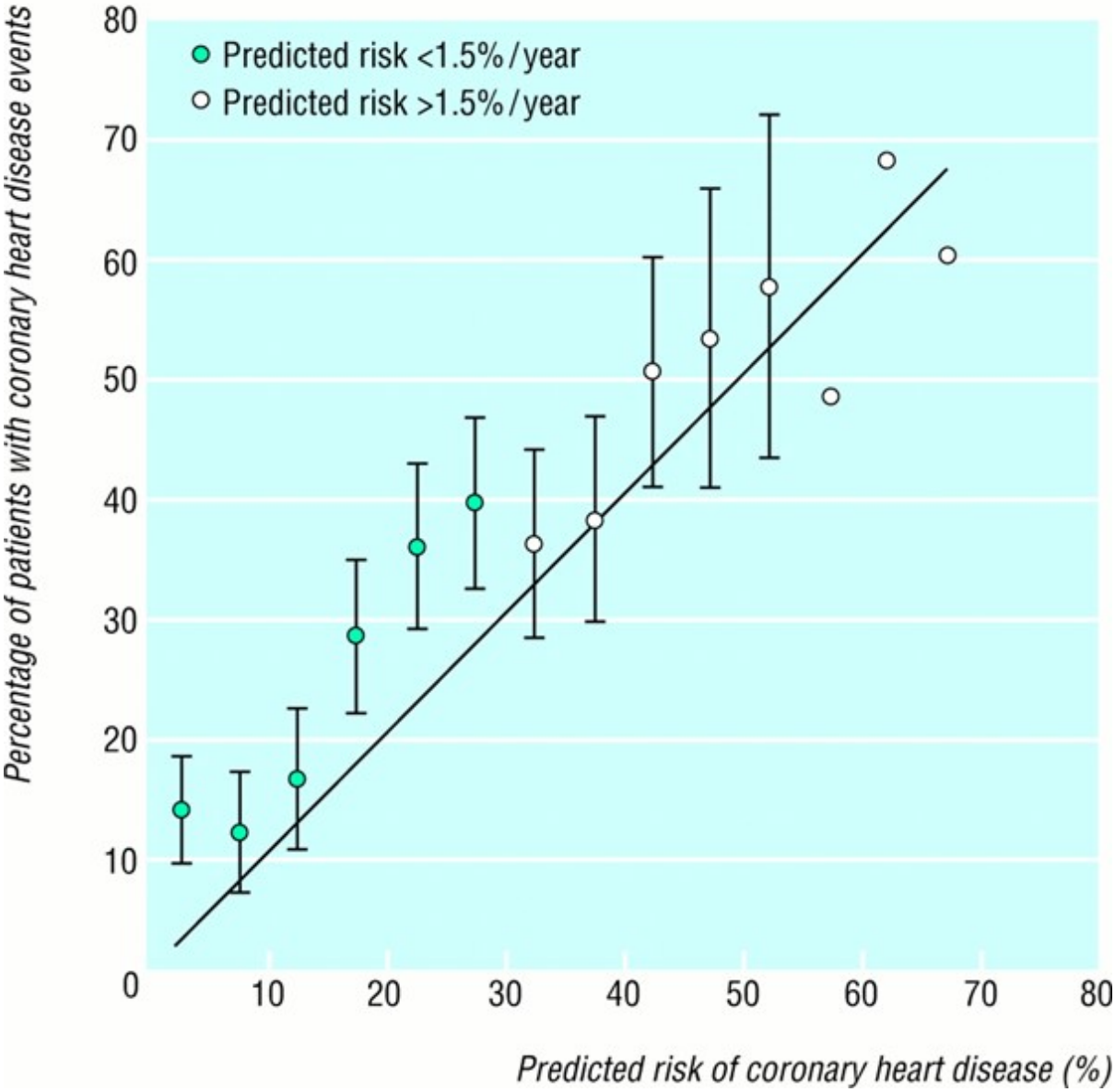
Figure 7 (Ramachandran 2000[215,215]) shows the number of coronary events predicted by the Framingham model and the number observed during follow up. The agreement is good at a predicted event rate above 30% (1.5% per year), with no significant difference between the observed and expected event rates (p=0.85). However, at lower event rates the 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.

Figure 7: Number of coronary heart disease events observed in the Whickham study compared with number of events predicted by Framingham model in participants with predicted risk below or above 1.5% per year.
(Ramachandran S et al. BMJ 2000;320:676-677[215,215]
©2000 BMJ Publishing Group Ltd)



Source: Ramachandran S et al. BMJ 2000;320:676-677[215,215]
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6.2.5 Reclassification data

Framingham versus QRISK2 (Hippisley-Cox 2008[116])

Of the 112,156 patients classified as high risk (risk of ≥20% over 10 years) with the Framingham score, 46,094 (41.1%) would be reclassified at low risk with QRISK2. The 10 year observed risk among these reclassified patients was 16.6% (95% CI: 16.1% to 17.0%).

Of the 78,024 patients classified at high risk with QRISK2, 11,962 (15.3%) would be reclassified as low risk with the Framingham score. The 10 year observed risk among these patients predicted to be at high risk with QRISK2 was 23.3% (95% CI: 22.2% to 24.4%).

The annual incidence rate of CV events among those with a QRISK2 score of ≥20% was 30.6 per 1000 person years (95% CI: 29.8 to 31.5) for women and 32.5 per 1000 person years (31.9 to 33.1) for men. Both these figures are higher than the annual incidence rate for patients identified as high risk with the modified Framingham score. The annual incidence rate for these patients was 25.7 per 1000 person years (25.0 to 26.3) for women with 26.4 (26.0 to 26.8) for men. In other words, at the 20% threshold, the population identified by QRISK2 was at higher risk of a CV event than the population identified by the Framingham score.

6.3 Economic evidence

Published literature

No relevant economic evaluations were identified that compared risk assessment tools for predicting the risk of CVD events in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease.

One economic evaluation relating to this review question was identified but was excluded due to methodological limitations.[266] This is listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow diagram in Appendix E.

6.4 Evidence statements

Clinical

- 24 studies (total n ranged from 428 to 3,601,918) reported considerable uncertainty as to whether there was any difference in discrimination amongst Framingham, QRISK2, UKPDS and age alone (high risk of bias).
- 4 studies (total n ranged from 500,000 to 3,601,918) reported an AUC between 77% and 84% for QRISK2; 20 studies (total n ranged from 428 to 3,601,918) reported an AUC between 59% and 80% for Framingham; 6 studies (total n ranged from 589 to 10,137) reported an AUC between 63% and 76% for UKPDS (high risk of bias).
- Two studies (total n ranged from 3853 to 6643) reported sensitivity between 10% and 38% and specificity between 79% and 95% for Framingham, 30% threshold, non-diabetic population (high risk of bias).
- Three studies (total n ranged from 6643 to 500,000) reported sensitivity between 37% and 68% and specificity between 74% and 91% for Framingham, 20% threshold, non-diabetic population (high risk of bias).
- Three studies (total n ranged from 6643 to 500,000) reported sensitivity between 75% and 79% and specificity between 55% and 80% for Framingham, 15% threshold, non-diabetic population (high risk of bias).

- One study (total n=10,137) reported sensitivity of 86% and specificity of 30% for Framingham, and sensitivity of 94% and specificity of 31% for UKPDS, 20% threshold, diabetic population (low risk of bias).
- One study (total n=428) reported sensitivity of 86% and specificity of 33% for Framingham, and sensitivity of 89% and specificity of 30% for UKPDS, 15% threshold, diabetic population (high risk of bias).

Economic

- No relevant economic evaluations were identified.

6.5 Recommendations and link to evidence

Recommendation	8. Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]
Relative values of different outcomes	The clinical outcomes that the GDG wanted to predict were CV events, in particular CV mortality, non-fatal MI and stroke. The GDG considered calibration, discrimination and reclassification of risk assessment tools to be important. The GDG considered that any risk tool should accurately predict the number of individuals likely to have an event, that is it needs to be well calibrated; over- or under- prediction would lead to over- or under- treatment, which could result in significant harm. Discrimination is important to correctly classify individuals into risk groups to inform decisions on pharmacological treatment. The GDG noted that reclassification indices are being used in comparing the performance of different risk tools around decision thresholds. The reclassification index is the difference between people re-classified to high risk or low risk, but it can be calculated in different ways and the absolute magnitude of changes is relevant as well as the difference. There is lack of agreement on the definition of reclassification index. The clinical reclassification index, based on clinically relevant re-classification decisions should also be considered.
Trade-off between clinical benefits and harms	One purpose of risk assessment is to decide on suitability for treatment. The GDG considered that the use of an appropriate assessment tool is unlikely to harm an individual patient but were concerned that emphasis on a risk assessment tool might distract from the need to use clinical judgement to inform interpretation of the tool according to the circumstances of each individual patient. Over-prediction will result in unnecessary treatment and anxiety, whereas under-prediction means a person would not be offered potentially preventative treatment. The evidence indicated that all the tools considered are better than chance at predicting risk. In terms of discrimination, QRISK2 and Framingham did not show significant differences from each other. QRISK2 shows better performance in terms of calibration and reclassification than Framingham: Framingham has a constant over-prediction of about 5% while QRISK2 shows agreement between the observed risk and the predicted risk up to about 30% CV risk[54]; 41% of people classified at high CV risk (of ≥20% over 10 years) with Framingham would be reclassified at low risk with QRISK2 while 15% of people classified at high CV risk with QRISK2 would be reclassified at low risk with Framingham.[116]
Economic considerations	No relevant economic evidence was identified assessing the cost effectiveness of using different risk assessment tools or strategies. The cost effectiveness of using different tools might vary if the resources needed to implement these tools were different – for example if one tool required more information, and if this would involve a greater number or length of appointments or a greater number of blood tests to be carried out to elicit the required information. However, that is not the case in this situation. Framingham risk assessment does

require fewer pieces of information than QRISK2 (for example, it does not require ethnicity, BMI or family history of CVD to be recorded), however, these are risk factors which can all either be measured easily or can be elicited quickly by asking the patient. They are also factors which general practices routinely record, for example on initial registration with the surgery, and are routinely held in electronic medical records. If this information is not recorded for an individual then the practice would usually seek to gather it at any available opportunity even if not needed immediately for the specific purpose of CV risk assessment.

The use of an age-alone strategy is subject to the same consideration, as most risk factors are not needed to carry out age-alone risk assessment but would still be of interest to the practice and could be collected easily. Age-alone risk assessment would however not require the collection of a blood sample to measure blood lipid levels, which is required for risk assessment using either QRISK2 or Framingham. However, once a decision is made to initiate statin treatment, a blood test would then be needed to measure baseline levels of blood lipids and to check liver transaminase levels. In this case, the resource use has shifted from before to after the risk assessment, and so there is a potential for cost saving. However, that would only apply to those individuals aged old enough to qualify for consideration for statin treatment who agree to attend a consultation to discuss this but then decline to initiate statin treatment. Given the low costs of these blood tests that would be a very small saving.

An age-alone strategy could in theory be adopted with fewer initial consultations, as all those in the relevant age groups could be informed by letter that they were recommended for treatment. However, the GDG agreed that this would be incompatible with the requirement for clinicians to carefully discuss with people the risks and benefits of statin treatment, to allow each individual the opportunity to consider whether they wish to receive such treatment. The GDG also believed that offering statin treatment widely, without personal face-to-face contact would lead to low rates of uptake of treatment. Such appointments also give GPs opportunities to discuss lifestyle risk factors with individuals, and to encourage additional interventions or behaviours to reduce those risk factors. Therefore an age-alone strategy would not lead to cost savings through fewer consultations.

Given that there does not appear to be any reason to expect significant differences in resource use in carrying out risk assessment, whatever risk tool or system is used, the cost effectiveness of using a risk assessment tool will therefore be related to its effectiveness in correctly predicting risk. The tool which best predicts true cardiovascular risk will minimise over-treatment of those actually at lower risk but wrongly classified by the tool as over the threshold adopted, and minimise under-treatment of those actually at higher risk but wrongly classified by the tool as under the threshold adopted.

As the QRISK2 tool was found to perform better than Framingham tools in terms of calibration and reclassification, it would hence also be more cost effective to treat people on the basis of their QRISK2 scores than on the basis of Framingham scores.

Regarding an age-alone strategy, the only effectiveness evidence available came from a simulated cohort, which found it to be almost as effective as Framingham. Evidence for an age-alone strategy in real world populations was not available. As noted in 'Other considerations' below, the largest problem with an age-alone strategy would be that people below the age threshold but at raised risk due to multiple other risk factors would not receive treatment despite it being clinically beneficial and cost effective for them to do so. Thus an age-alone strategy would be expected to be less cost effective overall than using the QRISK2 tool.

A potential combination of an age-alone strategy above an age threshold and a risk assessment strategy using QRISK2 below the threshold would produce a very similar outcome to the use of QRISK2 at all ages, and thus would be similar in cost effectiveness – though with perhaps a small amount of inefficient over-treatment of those who were above the age threshold but had a relatively low level of risk due to having no other risk factors – but it would have the downside of being a more

	complicated approach.
Quality of evidence	Framingham is based on a prospective cohort study (the gold standard), but in the USA. Inter-cohort heterogeneity exists in the 6 studies that validate Framingham-Anderson (1991) equation in the UK. Calibration data are only available for 3 studies. Calibration is updated about every 3 years on the basis of a US cohort, but would also need to be re-calibrated specifically for the UK. QRISK2 is derived in the UK from a large database of GP records. There is a large amount of missing data that is dealt with in development of the tool by imputation. QRISK 2 has been externally validated in another UK population cohort. QRISK2 is updated every year. QRISK2 performs better than Framingham in terms of AUC, R^2, D statistics and Brier score and is also better calibrated to UK CVD event rates.
Other considerations	**Other risk assessment tools** In their discussion, the GDG considered tools that had external validation in England and Wales. ASSIGN was developed in Scotland as part of the Scottish CV study. It is similar to QRISK2 and it includes the similar risk factors but with slightly different weighting coefficients. The GDG decided not to consider this tool because the deprivation score uses postcodes specific to Scotland with no easy method to correlate these with the England and Wales population. During the development of the guideline the Joint British Societies (JBS) published consensus recommendations for the prevention of cardiovascular disease. This includes a tool based on QRISK Lifetime. The JBS3 recommendations are to treat people with lifestyle advice and drugs according to their 10 year absolute risk and to use the lifestyle risk tool for information and education particularly in people[126] whose risk is lower than the threshold for drug treatment. **Lifetime risk versus 10-year risk** The GDG considered that lifetime risk and 10-year risk tools exist for both Framingham and QRISK2. The different versions identify different populations as being at risk. The GDG reviewed the evidence and the statistical techniques used to validate the performance of different risk tools. The GDG considered that lifetime risk tools should not be considered. Expert advice was that there are technical methodological issues with how to derive,[173] validate and present prognostic quantification of the outputs of these tools compared with the outputs of 10-year risk tools. Ten-year risk was also considered more relevant to whose risk could most profitably be reduced by any interventions and in particular when prescribed drug interventions should start. **Threshold for treatments** This guideline recommends risk assessment for the introduction of lipid modification but other guidelines also cross-refer to this guideline, for example Hypertension (CG127). At the time the clinical review was carried out, the threshold for treatment for lipid modification was not known. The Hypertension guideline recommends deciding on drug treatment in people with stage 1 hypertension if the 10-year CVD risk is 20% or more.[173] The review reported on metrics at risks of 5%, 10%, 15% and 20% where available, however, the majority of the evidence reported sensitivity and specificity of the tools at 15%, 20% and 30%. Following the health economics modelling, the GDG have chosen 10% 10-year CV risk as measured by QRISK2 as the threshold for offering drug therapy. None of the included studies reported data on this specific threshold; only one study (Wald 2011), based on a simulated population, reported sensitivity and specificity using thresholds of 8% and 5% CV risk as measured by Framingham-Anderson, concluding that at these thresholds the performance of Framingham is comparable to an assessment strategy based on age alone, with cut-off ages of 55 years and 50 years respectively. **Age screening** The GDG had requested information on age screening as part of this review. They acknowledged that since age is the most important contributor to CVD risk, an age-alone strategy would identify most people at risk. The GDG were concerned however

	that an age-alone strategy would not allow identification of people with increased risk at a younger age whose risk is increased by ethnicity, comorbidity or lifestyle factors. Younger people will also gain from treatment over a longer time period. The only evidence available for age is from a simulated cohort. The GDG considered it worthwhile to develop a research recommendation to use a prospective cohort to compare age and other simplified methods of risk assessment with validated risk tools. QRISK 2 has an upper limit of 84 years. All people of 85 years and older are at high risk of CVD by virtue of age alone. Decisions about interventions should be made on a clinical basis according to proposed treatments and other factors such as comorbidities and patient choice. **QRISK2 and Framingham derivation cohorts** One of the disadvantages of QRISK2 is that the databases from which it is developed will include people already on drug treatment such as antihypertensive treatment. The Framingham cohorts are more representative of people in whom treatment has not yet been initiated. Framingham will therefore overestimate observed risk in a modern population yet may provide better information on risk before any treatment is initiated. **Ease of use of QRISK2 and Framingham** As the risk tools are to be widely used, it is essential that both are easily available to potential users. The GDG noted that both tools are available electronically in GP practices and as web applications for other users. **Frequency of risk assessment** The GDG discussed whether it was appropriate to recommend how often risk assessment should be carried out. Risk assessment is currently mandated to be performed every 5 years as part of the NHS Health Check programme. The most significant CVD risk factor driving any transition to treatment using a risk tool is age. While multiple determinations of individual CVD risk factors at any single time point improve the accuracy of risk assessment, repeated risk assessments (such as annual checks) are not likely to be clinically useful given the errors involved in the process. Any significant changes in family history or knowledge of family history might necessitate a repeat of risk assessment.

Recommendation	**9. Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes. See recommendations 59, 60 and 61 for advice on treatment with statins for people with type 1 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.1.2 from Type 1 diabetes (NICE clinical guideline 15).]**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were CV events, in particular CV mortality, non-fatal MI and stroke. The GDG considered calibration, discrimination and reclassification of risk assessment tools to be important. The GDG considered that any risk tool should accurately predict the number of individuals likely to have an event, that is it needs to be well calibrated; over- or under- prediction would lead to over- or under- treatment, which could result in significant harm. Discrimination is important to correctly classify individuals into risk groups to inform decisions on pharmacological treatment. The GDG noted that reclassification indices are being used in comparing the performance of different risk tools around decision thresholds. The reclassification index is the difference between people re-classified to high risk or low risk, but it can be calculated in different ways and the absolute magnitude of changes is relevant as well as the difference. There is lack of agreement on the definition of reclassification index. The clinical reclassification index, based on clinically relevant re-classification

	decisions should also be considered. No suitable risk assessment outcome tool was identified for CV events in type 1 diabetes in a UK population.
Trade-off between clinical benefits and harms	One purpose of risk assessment is to decide on suitability for treatment. Over-prediction will result in unnecessary treatment and anxiety, whereas under-prediction means a person would not be offered potentially preventative treatment. The GDG considered that the use of an appropriate assessment tool is unlikely to harm an individual patient. . No evidence was found on the development of a specific substantially validated CV risk assessment tool for people with type 1 diabetes in a UK population.
Economic considerations	No economic evidence was identified relating to people with type 1 diabetes. Unless the use of a different tool requires different resource use in terms of numbers of appointments or blood tests carried out, which does not appear to be the case, the cost effectiveness of using a risk assessment tool will be largely related to its effectiveness in correctly predicting risk and so minimising over- and under-treatment. As the effectiveness of risk tools in this population is unknown, it is not possible to judge the cost effectiveness of using such tools in this population.
Quality of evidence	No evidence was found for the type 1 diabetes population; the recommendation is based on GDG expert opinion and consensus.
Other considerations	The GDG noted that CV risk is elevated in epidemiological and cohort studies of patients with type 1 diabetes. This has been confirmed in a population cohort study that included UK patients. Clinically type 1 and type 2 diabetes are different conditions. Epidemiological studies show a different rank-order for the significance of individual CV risk factors in type 1 and type 2 diabetes. In addition the evidence that exists in type 1 diabetes is mostly based on surrogate outcome measures of atherosclerosis rather than large scale CV event data. These studies identify features of the metabolic syndrome as highly relevant to the occurrence of CV events in type 1 diabetes and consistently identify waist-hip ratio allied with triglycerides and HDL cholesterol (also non-HDL cholesterol) as significant risk factors. The GDG considered that specialists in diabetes will recognise these risk factors and treat people accordingly. QRISK2 does include a tick box for type 1 diabetes. This however provides just a yes/no answer and does not include factors considered clinically important such as length of time patient has had diabetes. The GDG noted that there is no validation or calibration data regarding how QRISK2, or any other risk tool, performs for people with type 1 diabetes. The GDG concluded that no risk assessment tool could be applied to patients with type I diabetes but that they are likely to meet clinical criteria for having a CV risk substantially in excess of the general population of the same age and gender. The GDG considered it useful to cross-refer to the recommendations on treatment with statins in people with Type 1 diabetes.

Recommendation	**10. Use the QRISK2 risk assessment tool to assess CVD risk in people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendations 1.9.1 – 1.9.3 from Type 2 diabetes (NICE clinical guideline 87).]**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were CV events, in particular CV mortality, non-fatal MI and stroke. The GDG considered calibration, discrimination and reclassification of risk assessment tools to be important. The GDG considered that any risk tool should accurately predict the number of individuals likely to have an event, that is it needs to be well calibrated; over- or under- prediction would lead to over- or under- treatment, which could result in significant harm. Discrimination is important to correctly classify individuals into risk groups to inform decisions on pharmacological treatment.

	The GDG noted that reclassification indices are being used in comparing the performance of different risk tools around decision thresholds. The reclassification index is the difference between people re-classified to high risk or low risk, but it can be calculated in different ways and the absolute magnitude of changes is relevant as well as the difference. There is lack of agreement on the definition of reclassification index. The clinical reclassification index, based on clinically relevant re-classification decisions should also be considered.
Trade-off between clinical benefits and harms	One purpose of risk assessment is to decide on suitability for treatment. Over-prediction will result in unnecessary treatment and anxiety, whereas under-prediction means a person would not be offered potentially preventative treatment. The evidence indicated that all the tools considered are better than chance at predicting risk. The GDG considered that the use of an appropriate assessment tool is unlikely to harm an individual patient but were concerned that emphasis on a risk assessment tool might distract from the need to use clinical judgement to inform interpretation of the tool according to the circumstances of each individual patient.
Economic considerations	No economic evidence was identified relating to people with type 2 diabetes. Unless the use of a different tool requires different resource use in terms of numbers of appointments or blood tests carried out, which does not appear to be the case, the cost effectiveness of using a risk assessment tool will be largely related to its effectiveness in correctly predicting risk and so minimising over- and under-treatment. As the QRISK2 risk engine is felt to be likely to be the most clinically appropriate tool it is also likely to be cost effective compared to any other option.
Quality of evidence	Three studies carried out head-to-head comparisons of UKPDS versus Framingham, and the quality of the evidence ranged from low to high risk of bias. The UKPDS is based on a historical cohort and has not been updated. QRISK2 has the option to select type 2 diabetes as risk factor. The derivation and external validation of QRISK2 studies are at high risk of bias. Although there are no external validation studies of QRISK2 in the type 2 diabetes population, the development cohort of QRISK2 includes more than 40,000 patients with prevalent type 2 diabetes within primary care, compared to the 4540 patients newly diagnosed with type 2 diabetes that form the UKPDS derivation cohort.
Other considerations	Multiple epidemiological cohort studies and the evidence review of randomised clinical trial studies have established that CVD event rates are increased in patients with type 2 diabetes compared with the general population. Epidemiological studies of CV risk in type 2 diabetes have shown a strong relationship with LDL cholesterol and non-HDL cholesterol. The GDG discussed the concept of CVD risk equivalence in people with type 2 diabetes. This is the idea that risk in people with type 2 diabetes is elevated to the same extent that risk is elevated in people who have evidence of CVD. The GDG considered that the risk is not quite as high as in people being treated for secondary prevention and that use of a risk tool should be considered for the type 2 diabetes populations. The GDG considered that QRISK2 is updated annually and takes into account the changing prevalence of CVD risk factors such as obesity. It is also in common usage across the NHS and well integrated into the GP computer systems. The use of the same risk tool in people without diabetes and people with Type 2 diabetes who are being treated for primary prevention will aid implementation of risk screening strategies.

Recommendation	**11. Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria[c]. These people are at increased risk of CVD. See recommendation 62 for advice on treatment with statins for people with chronic kidney disease. [new 2014]**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were CV events, in particular CV mortality, non-fatal MI and stroke. The GDG considered calibration, discrimination and reclassification of risk assessment tools to be important. The GDG considered that any risk tool should accurately predict the number of individuals likely to have an event, that is it needs to be well calibrated; over- or under- prediction would lead to over- or under- treatment, which could result in significant harm. Discrimination is important to correctly classify individuals into risk groups to inform decisions on pharmacological treatment. The GDG noted that reclassification indices are being used in comparing the performance of different risk tools around decision thresholds. The reclassification index is the difference between people re-classified to high risk or low risk, but it can be calculated in different ways and the absolute magnitude of changes is relevant as well as the difference. There is lack of agreement on the definition of reclassification index. The clinical reclassification index, based on clinically relevant re-classification decisions should also be considered.
Trade-off between clinical benefits and harms	One purpose of risk assessment is to decide on suitability for treatment. Over-prediction will result in unnecessary treatment and anxiety, whereas under-prediction means a person would not be offered potentially preventative treatment. The evidence indicated that all the tools considered are better than chance at predicting risk. The GDG considered that the use of an appropriate assessment tool is unlikely to harm an individual patient but were concerned that emphasis on a risk assessment tool might distract from the need to use clinical judgement to inform interpretation of the tool according to the circumstances of each individual patient.
Economic considerations	No economic evidence was identified relating to people with CKD. Unless the use of a different tool requires different resource use in terms of numbers of appointments or blood tests carried out, which does not appear to be the case, the cost effectiveness of using a risk assessment tool will be largely related to its effectiveness in correctly predicting risk and so minimising over- or under-treatment. As the QRISK2 tool is felt to be likely to be the most clinically appropriate tool it is also likely to be cost effective compared to any other option.
Quality of evidence	No evidence was found specific to the CKD population; the recommendations are based on GDG consensus and expert opinion.
Other considerations	The GDG were joined by a co-opted expert in kidney disease for discussion of assessment of risk and treatment of people with CKD. The GDG agreed that people with a significant degree CKD are at increased CVD risk based on epidemiological studies and the event rate data for the subgroups with renal impairment in the evidence review of clinical trial populations. CV death in later stages of renal disease is however likely to be related to non-atherosclerotic disease such as arrhythmias. The classification of CKD is complicated. The NICE guideline on Chronic Kidney Disease suggests that people with eGFR greater than 60mls/min/1.73m^2 but without albuminuria should not be considered to have chronic kidney disease as they do not have evidence of kidney damage. However those with albuminuria are considered to have CKD whatever their eGFR and are at increased risk of progressing to more severe kidney disease. The presence of albuminuria is also associated with increased risk of CVD when albuminuria is greater than 3mg/ mmol creatinine. The GDG noted that QRISK2 does provide a tick box for “CKD”. This however is potentially misleading because it does not distinguish amongst grades of eGFR and

[c] People on renal replacement therapy are outside the scope of this guideline.

	albuminuria and includes under this heading quite different renal pathological processes that could generically be called 'kidney disease', for example pyelonephritis. People with albuminuria or with eGFR <60 ml/min/1.73m^2 with or without albuminuria should be considered to be at greater risk of CVD. CVD risk modification should be considered and the GDG considered it helpful to cross-refer to the recommendations on treatment with statins.

6.6 Recommendations [2008]

Recommendations	**12. Complete as many fields of the risk assessment tool as possible. [new 2014]** **13. Routinely record ethnicity, body mass index and family history of premature CVD in medical records. [2008]** **14. Consider socioeconomic status as an additional factor that contributes to CVD risk. [2008]** **15. Do not use a risk assessment tool for people with pre-existing CVD. [2008, amended 2014]** **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]** **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]** **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]** **19. Recognise that CVD risk will be 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]** **20. Severe obesity (body mass index greater than 40 kg/m^2) increases CVD risk. Take this into account when using risk scores to inform treatment decisions in this group (see Obesity [NICE clinical guideline 43]). [2008]** **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]**

2008

6.7 Research recommendation

Simplifying risk assessment

1. **What is the effectiveness of age alone and other routinely available risk factors compared with formal structured multi-factorial risk assessment to identify people at high risk of developing CVD?**

2. **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 age against validated simplified and complex CVD risk tools in prediction of people at high risk.

7 Communication about risk assessment and treatment [2008]

7.1 Introduction

Risk communication is defined as 'the open, two-way exchange of information and opinion about risk, leading to better decisions about clinical management'.[79] Discussing risk with patients in the clinical consultation has become increasingly important. Patients who are better informed and involved in decisions about their own care are more knowledgeable and also more likely to adhere to their chosen treatment plan.[102,202] Patients' values and preferences vary widely, as do their attitudes to risk. A two-way exchange of information is therefore important to explore the patient's personal beliefs to facilitate treatment decisions. 2008

Communication of risk is not straightforward. Clinicians need to support patients in making choices by turning raw data into information that can be used to aid discussion of risk. Decisions aids are one way of facilitating this process. Decision aids are systematically developed tools to aid patients to understand and participate in medical decisions. Decision aids often include visual representations of risk information and relate this information to more familiar risks. They can be in the form of booklets, DVDs, interactive computer programmes, tapes or web-based products. There is, however, very little evidence of the effectiveness of these aids in communicating risk in patients at high cardiovascular risk.

Update 2014

NICE developed a guideline on Patient experience in adult NHS services in 2012 (NICE clinical guidance 138). This guideline includes recommendations on discussion of risk and benefit with patients and is cross-referred to by this guideline.

7.2 Clinical effectiveness of methods of communicating risk assessment to individuals at high risk of cardiovascular disease (CVD)

The use of decision aids in people facing health treatment or screening decisions has been examined in a systematic review.[202] The review had two aims: firstly to document an inventory of decision aids focused on healthcare options and secondly to review randomised controlled trials of decisions aids for people contemplating healthcare decisions. The systematic review also examined studies that compared simpler decision aids with more detailed decision aids.

The systematic review identified over 200 decision aids, of which 131 were available for review. Most of these were intended to be used as a preparation for counselling about an important decision. Ninety-four were web-based, 14 were paper based, 12 were videos, 8 were audio-guided print resources, 2 were CD-ROMS and 1 was web-based with a workbook. Analysis of the quality of these aids found that the majority included potential harms and benefits, update policy, description of the development process, credentials of the developers, reference to relevant literature and were free of perceived conflict of interest. However, few decision aids contained a description of the level of uncertainty regarding the evidence, and few had been validated.[202] 2008

Thirty of the decision aids that were identified in the inventory were assessed in 34 randomised controlled trials. The majority of these studies evaluated decision aids for people considering cancer screening, cancer therapy, and genetic testing or hormone replacement therapy. Examples of the type of decision aid that were compared with usual care are as follows: an audiotape and a booklet, a pamphlet alone, a pamphlet plus a discussion with a healthcare professional, a series of 8 pamphlet

decision aids, an interactive video, and a video plus a booklet [202]. No randomised controlled trials were identified that examined decision aids in the communication of cardiovascular risk in people at high risk of developing CVD.

To determine whether the decision aids achieved their objectives a range of positive and negative effects on the process of decision making, and on the outcomes of decisions were evaluated. Although the decision aids focused on diverse clinical decisions, many had similar objectives. The outcomes were specified in advance of the review and included; knowledge, realistic expectations, decisional conflict relating to feeling informed, the proportion of people active in decision making, the proportion of people who remain undecided concerning their treatment options and choice, satisfaction with the decision aids, anxiety, and health outcomes following use of the decision aids.[202]

The studies' knowledge tests were based on information contained in the decision aid, thereby establishing content validity. The authors of the systematic review transformed the proportion of accurate responses to a percentage scale ranging from 0% (no correct responses) to 100% (perfectly accurate responses). Perceived outcome probabilities (a measure of a measure of realistic expectation) were classified according to the percentage of individuals whose judgments corresponded to the scientific evidence about the chances of an outcome for similar people. Decisional conflict was assessed using the previously validated Decisional Conflict Scale [201]. The scale measures the constructs of uncertainty and factors contributing to uncertainty (such as feeling uninformed, unclear about values, and unsupported in decision making). The scores were standardised to range from zero (no decisional conflict) to 100 points (extreme decisional conflict). Scores of 25 or lower are associated with follow-through with decisions, whereas scores that exceed 38 are associated with delay in decision making. When decision aids are compared to usual care, a negative score indicates a reduction in decisional conflict, which is in favour of the decision aid.[202]

Compared with usual care, the use of decision aids was found to increase knowledge in all of the included studies. The gains ranged from 9 to 30 percentage points and the weighted mean difference (WMD) was 19 out of 100 (95% CI 13 to 24), Decision aids increased the perceived probabilities of outcome which was a measure of realistic expectation (RR 1.4, 95% CI 1.1 to 1.9). Decisional aids decreased decisional conflict in all of the included studies, and ranged from -2 to -10 out of 100 with a WMD of -9.1 out of 100 (95% CI -12 to -6). Compared with usual care, decisional aids increased the proportion of people active in decision making (RR 1.4, 95% CI 1.0 to 2.3), and reduced the proportion of people who remain undecided concerning their treatment options (RR 0.43, 95% CI 0.3 to 0.7). The authors commented that the findings were important for two reasons. Firstly, people's level of knowledge and perception of health outcomes in the usual care groups appeared insufficient for informed decision making. Secondly, people's healthcare treatment choice often changed once their knowledge and realistic expectation scores improved. Overall, these findings indicate that 'usual care' may be inadequate when people are facing complex value-laden decisions. These findings also suggest that people need to comprehend the options and probable outcomes to aid in their own decision making. Decision aids also may help people to communicate to their clinicians the personal value they place on the benefits versus the harms.[202]

2008

Compared with usual care, the use of decision aids did not generally increase satisfaction with decision making, nor did their use reduce anxiety. Decision aids also did not have a consistent effect on general health outcomes. The authors noted that measurement of satisfaction is liable to insensitivity because it is more likely to be linked to the relationship of an individual with the clinician than with the decision aid. Also, satisfaction with usual care may already be high. Anxiety as an outcome measure was deemed inappropriate by the author because more effective decision strategies are associated with a moderate increase in anxiety. The predominately null effect of decision aids for health outcomes suggest that rates of actual choices can vary without affecting quality of life. However, the author suggested that in future studies it may be more appropriate to link the measurement of health outcomes to prior patient choices to provide a more accurate determination of the effect of decision aids because this was not done in the trials identified.[202]

In summary, compared with usual care strategies, the systematic review found that decision aids consistently improved an individual's involvement in decision making. The review had a number of limitations in that there was variability in the decision contexts, variability in the design of the decision aids (content, format, and use), and in the type of comparison. The choice of the decision aid will depend upon the needs of the individual (for example literacy, motivation), the nature of the intervention to be explained and considered, and also upon the expectations of clinicians.[202]

For the comparison of simpler decision aids and more detailed decision aids the majority of the included studies had defined the simpler decision aid as pamphlets. Examples of the more detailed decision aids included an audiotape booklet, an audiotape booklet with values clarification, an interactive DVD, a pamphlet plus a video plus a decision tree, and a lecture plus a personal decision exercise.[202]

Compared with simpler decision aids, the use of more detailed decision aids were found to marginally improve knowledge (4 out of 100 (WMD), 95% CI 3 to 6) and more realistic expectations (RR 1.5, 95% CI 1.3 to 1.7). Detailed decision aids appeared to do no better than comparisons in affecting satisfaction with decision making, anxiety, and health outcomes. There was a variable effect of detailed decision aids on whether a healthcare option under study was selected. Some studies found that detailed decision aids increased the uptake of a healthcare option compared with simpler decision aids, while others did not.[202]

The authors stated that the small differences in knowledge scores between detailed and simpler versions of decision aids are likely due to the overlapping information presented in the two interventions. In contrast, the effects remained large for expectation measures and for agreement between values and choice. These observations may occur because the detailed interventions, in contrast to the simpler versions, generally contained probabilistic information about outcomes as well as explicit values clarification exercises. The authors also noted that the effect of providing different components of decision support within decision aids was not examined due to lack of available data. The issue of what to include in a decision aid remains unresolved. There is a need to establish the 'essential ingredients' in decision aids and to identify the people who are most likely to benefit from detailed versions.[202]

2008

A second systematic review[29] (Appendix K of CG67) identified two randomised controlled trials that assessed the impact of different risk scoring methods on clinical outcomes in populations mainly without a history of CVD.[111,112,171] Both studies used patients with a pre-defined diagnosis of hypertension.

The first used a cluster randomised controlled trial design with 614 patients from 27 practices in Avon. Three different methods of delivering risk factor scoring systems to clinicians were assessed: a computerised clinical decision support system (CDSS) plus cardiovascular risk chart; cardiovascular risk chart alone; or usual care.[171]

No differences were found between the CDSS plus chart group and the usual care group in terms of change in 5 year risk, change in systolic and diastolic blood pressure and odds ratios for taking 2 or 3 or more classes of drugs compared with 0 or 1. The chart-only group did have significantly lower systolic blood pressure (at 6 months) and were more likely to be prescribed cardiovascular drugs (at 12 months) compared with the usual care group. People with 5-year CVD risk > 20% were more likely to reduce their risk in the chart or computer group than in usual care. The extent to which each group adopted the use of CDSS or charts is not clear. The authors of the study suggested that the CDSS may confuse or distract the healthcare professional in their use of the chart.[171]

The second study used a cluster randomised controlled trial design with GPs from 17 Norwegian health centres either being offered CDSS or practising usual care. They found no clinically significant difference in blood pressure or total cholesterol between the two groups at the end of the follow-up period of 21 months.[111,112]

Regarding the quality of the studies, both used cluster randomisation and participants were not blinded to their group. In addition, the first reported losses of 14% at 12 months.[171] The second study did not conduct a power calculation or report confidence intervals. [111,112]

Regarding the effectiveness of CDSS, one study showed no clinically significant differences versus usual care but did note that despite an average of 1.5 hours of training, uptake of CDSS in the intervention group was only 12%.[111,112] The other study showed a negative effect on systolic blood pressure when CDSS was added to a risk-chart and a greater reduction in risk in people at high risk. No data were available on the uptake rate.[171] It has been suggested that the inclusion of clinicians in the design of decision aids may improve their use[35,36] and also that paper-based cardiovascular risk tables are inaccurately used.[207]

In summary, these two studies showed limited or no difference between groups advised to use CDSS and those providing usual care except in people at highest risk. One study indicated uptake of CDSS was very low.[111,112]

A pilot randomised trial has assessed the impact of a decision aid about heart disease prevention in adults with no previous history of heart disease.[238,238] This was a small study; 75 people were enrolled and of these, 43% had a 10-year CVD risk of 0-5%, 25% a risk of 6-10%, 24% a risk of 11-20% and 5% a risk of > 20%. The intervention group was given the computerised decision aid 'Heart to Heart' (version 1). This calculates an individual's global risk of CVD events in the next 10 years by combining information on an individual's age, sex, blood pressure, total and HDL-cholesterol, smoking status, diabetes, and left ventricular hypertrophy status using a continuous Framingham equation. 'Heart to Heart' provides individualised information about an individual's global CVD risk, personal risk factors, the benefits and risks of CVD risk reducing therapies (e.g. hypertension therapy, lipid lowering treatment, aspirin), and the risk reductions achievable after one or more therapeutic interventions. 'Heart to Heart 'also encourages the individual to choose therapies that are feasible for long-term CVD risk reduction. In addition, the tool encourages the adoption of a good diet and exercise. The control group received only a list of their CVD risk factors that they could present at the clinical consultation. Forty-one people received the decision aid, and 34 people received the usual care.

2008

Self-reported data were collected at four points in a single study consultation: during initial eligibility assessment, at baseline, after navigation of the study aid (intervention group only), and after the regularly scheduled provider visit. The main effect of the decision aid on decision making was assessed by the proportion of participants who reported discussing their CVD risk with their clinician, and by the proportion of participants who had a specific plan for CVD risk reduction at the post-visit survey. Within-group effects of the decision aid were assessed using pre-post comparisons of an individual's perception that CVD prevention requires a decision, and the individual's desired participation in decision making. In unadjusted analysis, the decision aid increased the proportion of participants who discussed CVD risk reduction with their clinician (absolute difference 16%, 95% CI -4% to 37%) and increased the proportion who had a specific plan to reduce their risk from 24% to 37% (absolute difference 13%, 95% CI -7% to +34%).The authors stated that there were too few participants in the trial to perform adjusted analysis. In pre-post testing analysis, the decision aid appeared to increase the proportion of people with plans to intervene on their CVD risk (absolute increase ranging from 21% to 47% for planned medication use, and 5% to 16% for planned behavioural interventions).[238,238]

The authors concluded that the trial provides preliminary evidence that an individually tailored decision aid about CVD prevention may facilitate an individual's discussion of CVD risks with their healthcare professional, and also may facilitate in CVD risk reduction management plans.[238,238]

A narrative review has discussed the presentation of medical statistics to convey risks to people contemplating a healthcare decision.[102] Three specific numerical representations were identified that engender confusion, namely single event probabilities, conditional probabilities, and the use of relative risks.

Single event probabilities describe the chance of an event occurring in percentage form, for example 'there is a 5% chance that drug A will cause harmful side effect B'. Confusion can arise as some individuals may interpret this to mean that '5% of the time taking drug A will cause harmful side effect B'. The authors stated that an individual's perception of risk will be clearer if frequency statements are used that specify a reference class. For example, conveying the risk of harmful side effect B can be expressed as '5 out of every 100 people will have side effect B from taking drug A'.[102] Conditional probabilities, for example the sensitivity, specificity and a positive predictive value of a screening test, are often misunderstood. Sensitivity refers to the class of people with the illness, while specificity refers to those without the illness. Again, converting the percentage probability of a positive test and the percentage probability of an individual actually having an illness is better represented in the form of frequency statements.[102]

The use of relative risks can also be misleading. The numerical risk reduction value may be incorrectly linked to the intervention population, rather than the event rate in the population that does not receive the intervention. Misinterpretation of relative risks can result in perceived gross over-estimation of the effectiveness of an intervention. This confusion can be avoided by communicating absolute risk reductions either in the form of percentages or conversion into integers (such as a 1 in 10 chance).[102]

In summary the author concluded that single event probabilities, conditional probabilities and relative risks are confusing because they make it difficult to understand what class of events a probability or percentage refers to. The use of transparent representations (such as natural frequencies and absolute risks) clarifies the reference class and should aid in perception of risk.[102] It is also important to note that presentation of risk should be given with a specified time frame.[261]

The visual communication of risk has been extensively described by Lipkus and Hollands.[146] Visual displays such as graphs reveal data patterns that may be undetected in numerical information, and graphs can attract and hold people's attention because they display information in concrete, visual terms. To be useful, graphs must convey different risk characteristics such as risk magnitude, the comparison of the magnitude of two risks, cumulative risk (i.e. observing trends over time), uncertainty, and interactions into among different risk factors. A number of different graphical representations of risk have developed, but is important to note that there is little clinical trial evidence available of the effectiveness of graphs compared with numerical representation of risk. Graphs can be in the form of risk ladders (that displays a range of risk magnitudes such that increased risk is portrayed higher up in the ladder), stick and facial figures, line graphs, dots and related formats, pie charts and histograms. There is a suggestion that simpler bar charts are preferable to more complex representations of data (i.e. pie charts, crowd figures, survival curves).[261] It has been suggested that the combination of graphical and numerical risk may provide the best approach. However the visual and numerical communication of risk should be tailored to fit an individual's need.[261]

2008

7.3 Evidence statements – communication of risk assessment and information

There is limited evidence of the effectiveness of different methods of communicating risk of CVD to patients.

One small randomised controlled trial piloting a computerised decision aid has suggested that an individually tailored decision aid about coronary heart disease prevention may facilitate an individual's discussion of risks with their healthcare professional, and also may facilitate risk reduction management plans.

A systematic review of the use of decision aids in people facing health treatment or screening decisions has shown that compared with usual care, the use of decision aids:

- increase knowledge
- increase the perceived probabilities of outcome (a measure of realistic expectation)
- lower decisional conflict relating to feeling informed
- increase the proportion of people active in decision making
- reduce the proportion of people who remain undecided concerning their treatment options.

Descriptive studies suggest that:

- Numerical presentation of risk should present absolute risk of events rather than relative risk of events. Where absolute risks of events are unavailable, relative risk of events may be presented.
- Graphical presentation of risk may aid in the communication of risk.

2008

7.4 Evidence to Recommendations

A self-selected group from the GDG (including patient representatives) convened to discuss and formulate draft recommendations on the communication of risk assessment. The evidence and the draft recommendations from this subgroup were presented to the GDG. Recommendations were then made collectively. The GDG recognised that there was limited evidence in this important area The GDG made a research recommendation that there is a need for trial evidence on methods of improving risk communication and patient decision-making.

7.5 Recommendations

Recommendations	**22. NICE has produced guidance on the components of good patient experience in adult NHS services. These include recommendations on the communication of risk. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138). [new 2014]** **23. Use everyday, jargon-free, language to communicate information on risk. If technical terms are used, explain them clearly. [2008]** **24. Set aside adequate time during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required. [2008]** **25. Document the discussion relating to the consultation on risk assessment and the person's decision. [2008]** **26. Offer people 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:** • **presents individualised risk and benefit scenarios and** • **presents the absolute risk of events numerically and** • **uses appropriate diagrams and text. [2008]** **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)** • **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]** **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]**

2008

8 Cardioprotective diet

8.1 Introduction

CG67 included recommendations on lifestyle interventions such as diet, smoking and physical activity. The only area included in the scope for update in this area was dietary intervention strategies. As noted in the introduction to the chapter on lifestyle interventions in CG67, there is a body of epidemiological, physiological and observational evidence demonstrating that changes in diet are associated with reductions in morbidity and mortality from CVD. In keeping with CG67, we have limited formal searches for evidence to randomised trials with outcomes that include CV events.

8.2 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)?

For full details see review protocol in Appendix C.

Table 16: PICO characteristics of review question

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	• Diet
Comparison	• No intervention / usual diet
Outcomes	1. All-cause mortality 2. CV mortality 3. Non-fatal MI 4. Stroke and TIA 5. Adverse events 6. Quality of life
Study design	RCTs, SRs of RCTs

8.3 Clinical evidence

Fourteen studies were included in the review.[1,2,41,42,60,60,63-68,88,91,144,217,220,224,243,245,272,281]

Evidence from these are summarised in the clinical GRADE evidence profiles below (Table 23 to Table 32).

Seven studies compared a high polyunsaturated fat diet versus usual diet: Los Angeles Veteran Study 1969,[60,61] Minnesota Coronary Survey 1989,[91] Oslo Diet Heart Study 1966,[144,145] Research Committee MRC 1968,[2] Rose 1965,[224] Sydney Diet Heart Study 1978,[217,281] Singh 1991[245] (Table 17). Three studies compared a low fat diet versus usual diet: DART 1989,[41,42] Research Committee MRC 1965,[1] STARS 1992[272] (Table 18). One study compared a high fibre diet versus usual diet: DART 1989[41,42] (Table 19). Two studies compared an increased oily fish diet versus usual diet; DART 1989,[41,42] DART 2 2003[40]

(Table 20). One study compared an increased fruit and vegetable, and fibre versus usual diet; DART 2 2003[40] (Table 21). Three studies compared a Mediterranean diet versus usual diet: Indo-Mediterranean Diet Heart Study 2002,[243] Lyon Diet Heart study 1999,[63-68,220] PREDIMED 2013[88] (Table 22).

Two studies were in primary prevention populations: Minnesota Coronary Survey 1989,[91] PREDIMED 2013.[88] Three studies were in a mixture of primary and secondary populations: Los Angeles Veteran Study 1969,[60,61] Singh 1991,[245] Indo-Mediterranean Diet Heart Study 2002,[243] Nine studies were in secondary populations: Oslo Diet Heart Study 1966,[144,145] Research Committee MRC 1968,[2] Rose 1965,[224] Sydney Diet Heart Study 1978,[217,281] DART 1989,[41,42] Research Committee MRC 1965,[1] STARS 1992,[272] Lyon Diet Heart study 1999,[63-68,220] DART 2 2003.[40]

One Cochrane systematic review was identified on dietary interventions (Hooper 2011). It was excluded from this review because the inclusion criteria included populations that were outside the scope of this guideline.[119]

No evidence was identified for subgroups of; black and minority ethnic groups, people with a family history of CVD, low socioeconomic groups, people aged 75 years and over, and people with autoimmune disease. One study was found for people with serious mental illness and reported results for men and women separately (Minnesota Coronary Survey 1989[91]).

See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 17: Summary of included studies on increased polyunsaturated fat in diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
Los Angeles Veteran Study 1969[60,61]	• Increased polyunsaturated fatty acids; linoleic acid 4 times greater than usual diet and; ○ decreased saturated fat • Conventional American diet	n=846 Increased poly-unsaturated fat n=424 versus control n=422 USA	All-cause mortality CV mortality Non-fatal MI Stroke/TIA	8 years	Primary and secondary prevention (men aged ≥54 years)
Minnesota Coronary Survey 1989[91]	• Increased polyunsaturated fatty acids to provide 18-20% of calories ○ limit saturated fat to <9% ○ ratio polyunsaturated to saturated fat to >2:1 ○ total cholesterol ≤150 mg/day • Hospital and nursing home usual diet	n=9057 Increased poly-unsaturated fat n=4541 versus control n=4516 USA	All-cause mortality	4.5 years	Primary prevention (men and women in-patients with mental health problems in psychiatric hospitals)
Oslo Diet Heart Study 1966[144,145]	• Increased polyunsaturated fatty acids, total soy bean oil set at ½ litre per week and;	n=412 Increased poly-unsaturated fat n=206	All-cause mortality CV mortality	5 years	Secondary prevention (men after MI aged >30 to 64 years)

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
	○ advice to restrict meat and remove fat, avoid whole milk, cream, butter, one egg permitted per week • Usual diet	versus control n=206 Norway			
Research Committee MRC 1968[2]	• 85 g soya bean oil daily to increase polyunsaturated fat and saturated fats removed from the diet and ○ up to 35 g of other fat / day allowed, 14 g taken as moderately unsaturated margarine ○ lean meat (up to 85 g), any fish, skimmed milk, clear soups allowed ○ butter, other margarines, whole milk, cheese, egg yolk, biscuits and cakes were forbidden. • Usual diet	n=393 high poly-unsaturated fat n=199 versus control n= 194 UK	All-cause mortality CV mortality Non-fatal MI	6 years	Secondary prevention (men after first acute MI <60 years, men with diabetes excluded)
Rose 1965[224]	• Corn oil supplement 80 g/day to increase polyunsaturated fat ○ advice to avoid fried foods, fatty meat, sausages, pastry, ice cream and cakes ○ milk, butter and eggs restricted • Usual diet	n=54 (total study) corn oil supplement n=28 versus control n=26 UK	CV mortality Non-fatal MI	2 years	Secondary prevention (men after acute MI <70 years) Study reported 6/54 participants dropped out, and 4/54 participants were removed, with no details on which group
Sydney Diet Heart Study 1978[217,281]	• Increase polyunsaturated fat intake to 15% total diet and; ○ reduce intake of saturated fatty acids and dietary cholesterol to less than 10% ○ participants provided with liquid safflower oil and safflower polyunsaturated margarine • No specific advice, some participants substituted polyunsaturated margarine for butter	n=458 increase poly-unsaturated fat n=221 versus control n=237 Australia	All-cause mortality CV mortality	5 years	Secondary prevention (men after recent coronary event aged 30 to 59 years) The original dataset of the study conducted between 1966 to 1973 was recovered and more modern statistical analyses were performed, only variables that exactly matched published data were included
Singh 1991[245]	• Increase polyunsaturated fat intake by replacing	n=463 increase	All-cause mortality	1 year	Primary and secondary prevention (men and

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
	meat and eggs with following to ensure diet isocaloric and low in saturated fat; ○ fish or protein ○ fat rich cereals ○ cottage cheese • Usual diet	poly-unsaturated fat n=228 versus control n=230 India	Non-fatal MI Stroke		women) Study reported 5 participants dropped out, with no details on which group

Table 18: Summary of included studies on decreased fat in diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
DART 1989[41,42]	• Fat advice designed to reduce fat intake to 30% total energy, increase polyunsaturated / saturated ratio to 1:0 • No specific dietary advice, told to take a balanced diet	n=2033 (total study) fat advice n=1018 versus control n=1105 UK	All-cause mortality Non-fatal MI	2 years	Secondary prevention (men after acute MI <70 years, men with diabetes excluded) Decrease fat advice group included some participants advised to increase fibre, increase oily fish and decrease fruit and vegetables
Research Committee MRC 1965[1]	• Low fat diet; 40 g fat/day, daily allowance; ○ 14 g butter ○ 84 g meat ○ 1 egg ○ cottage cheese (unrestricted) ○ skimmed milk (unrestricted) • No alteration of diet unless overweight • Overweight individuals in both groups given reducing diet	n=252 low fat diet n=123 versus control n=129 UK	All-cause mortality CV mortality Non-fatal MI	Mean 5.05 years	Secondary prevention (men after first acute MI <65 years, men with diabetes excluded) Usual (no fibre) diet advice group included some participants advised to decrease fat, increase oily fish and increase fruit and vegetables
STARS 1992[272]	• 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	n=55 low fat diet n=27 versus control n=28 UK	All-cause mortality CV mortality Non-fatal MI Stroke	Mean (SD) 39(3.5) months	Secondary prevention (men after MI and /or angina, <65 years, men with diabetes excluded)

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
	equivalent of 3.8 g polygalacturonate / 1000 kcal • Usual diet				

Table 19: Summary of included studies on increased fibre in diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
DART 1989[41,42]	• Increase fibre designed to increase intake of cereal fibre to 18 g daily • Non-specific dietary advice, advised to take a balanced diet	n=2033 (total study) increased fibre diet n=1017 versus control n=1016 UK	All-cause mortality Non-fatal MI	2 years	Secondary prevention (men after acute MI <70 years, men with diabetes excluded) Increase fibre group included some participants advised to decrease fat, increase oily fish and increase fruit and vegetables Usual (no fibre) diet advice group included some participants advised to decrease fat, increase oily fish and increase fruit and vegetables

Table 20: Summary of included studies on increased oily fish in diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
DART 1989[41,42]	• Increase oily fish; at least 2 weekly portions (200-400 g) of fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, trout), or fish oil capsules if unable to tolerate fish versus • Non-specific dietary advice, advised to take a balanced diet	n=2033 (total study) oily fish diet n=257 versus control n=252 UK	All-cause mortality, stroke	2 years	Secondary prevention (men after acute MI <70 years, men with diabetes excluded) Extractable data was available for fish advice group only versus no advice group only (unlike other interventions in study in that the increased fibre group, the increased fruit and vegetable group and the reduced fat groups each included combinations of the other diets)

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
DART 2 2003[40]	• Advice to at least 2 weekly portions of oily fish, or fish oil capsules if unable to tolerate fish • Non-specific dietary advice, advised to have a sensible diet	n=3114 (total study) oily fish diet n= 764 versus control n=764 UK	All-cause mortality	36 to 108 months	Secondary prevention (men treated for angina <70 years) Recruitment occurred in 2 phases: Phase I was between 1990 and 1992 (1111 participants) and phase II (2003 participants) between 1993 and 1996 In second phase of study, 462 participants were sub-randomised to receive fish oil capsules, or advice to increase oily fish

Table 21: Summary of included studies on increased fruit and vegetables in diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
DART 2[40]	• Advice to eat 4-5 portions of fruit and vegetables and ○ drink one glass of orange juice daily ○ increase intake of soluble fibre in the form of oats (8 g daily) • Non-specific dietary advice, advised to have a sensible diet	n=3144 (total study) increased fruit and vegetable n=779 versus control n=764 UK	All-cause mortality	36 to 108 months	Secondary prevention (men treated for angina <70 years) Recruitment occurred in 2 phases: Phase I was between 1990 and 1992 and phase II between 1993 and 1996

Table 22: Summary of included studies on Mediterranean diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
Indo-Mediterranean Diet Heart Study 2002[243]	• 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 • Prudent diet • Both groups advised to eat substitutes providing a dietary intake similar to	n=1000 Mediterranean diet n=499 versus control n=501 India	All-cause mortality Non-fatal MI Stroke	2 years	Primary and secondary prevention (men and women)

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
	that recommended by the National Cholesterol Education Program in the step I prudent diet				
Lyon Diet Heart Study 1999[63-68,220]	• Mediterranean diet ○ 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 • Non-specific advice, advised to follow a prudent diet by physician or hospital dietitian	Mediterranean diet n=302 versus control n=303 France	All-cause mortality Non-fatal MI Stroke	46 months	Secondary prevention (men and women within 6 months of first MI aged <70 years)
PREDIMED 2013[88]	• Mediterranean diet with 50 g or more of supplied polyphenol-rich olive oil/day • Mediterranean diet with nuts (30 g mixed nuts/day: 15 g walnuts, 7.5 g walnuts, 7.5 g almonds) and abundant ordinary olive oil • Both Mediterranean diets given following advice: consumption of ≥ 2 daily servings of vegetables (at least 1 in a salad), ≥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	n=7447 Mediterranean diet supplement olive oil n=2543 Mediterranean diet supplement nuts n=2454 Control n=2450 Spain	All-cause mortality CV mortality Non-fatal MI Stroke	Median 4.8 years (IQR 2.8-5.8)	Primary prevention (men and women at high CV risk aged <70 years) Usual diet group was advised to reduce fat and some of its recommendations included components of a standard Mediterranean diet

Study	Intervention versus comparison	Population	Outcomes	Follow-up	Comments
	products (cakes, donuts, or cookies), industrial desserts (puddings, custard), French fries or potato chips, and out-of-home pre-cooked cakes and sweets • Advised to reduce fat and recommended consumption of ≥3 daily servings of; low fat dairy products, bread, pasta, potatoes, or rice, fresh fruit, ≥3 weekly servings of vegetables, ≥3 weekly servings of lean fish and seafood, the following were discouraged; vegetable oils (including olive oil, commercial bakery goods and sweets, red and processed fatty meats, visible fat in meats and soups, fatty fish, seafood canned in oil, spread fats, sauce made with tomatoes and olive oil				

Table 23: Clinical evidence profile: high polyunsaturated fat diet versus control diet in primary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High polyunsaturated fat diet - Primary prevention	Control	Relative (95% CI)	Absolute		
All-cause mortality (Minnesota Coronary Survey 1989[91])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	269/4541 (5.9%)	248/4516 (5.5%)	RR 1.08 (0.91 to 1.28)	4 more per 1000 (from 5 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality – Men (Minnesota Coronary Survey 1989[91])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	158/2197 (7.2%)	153/2196 (7%)	RR 1.03 (0.83 to 1.28)	2 more per 1000 (from 12 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality – Women (Minnesota Coronary Survey 1989[91])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	111/2344 (4.7%)	95/2320 (4.1%)	RR 1.16 (0.88 to 1.51)	7 more per 1000 (from 5 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL
Total stroke (Minnesota Coronary Survey 1989[91])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	5/4541 (0.11%)	8/4516 (0.18%)	RR 0.64 (0.22 to 1.88)	1 fewer per 1000 (from 1 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Total stroke – Men (Minnesota Coronary Survey 1989[91])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/2197 (0%)	4/2196 (0.18%)	RR 0.11 (0.01 to 2.06)	2 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Total stroke – Women (Minnesota Coronary Survey 1989[91])												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	5/2344 (0.21%)	4/2320 (0.17%)	RR 1.24 (0.33 to 4.6)	0 more per 1000 (from 1 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

[a]*Unclear allocation concealment, unclear if each arm had comparable care.*
[b]*The upper limit of the confidence interval for the effect size crosses the minimal important difference (1.25) making the effect size uncertain*
[c]*The lower and upper limit of the confidence interval for the effect size cross 2 default MIDs (0.75 and 1.25, respectively), making the effect size uncertain*

Table 24: Clinical evidence profile: high polyunsaturated fat diet versus control diet in primary and secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High polyunsaturated fat diet - Primary and secondary prevention	Control	Relative (95% CI)	Absolute		
All-cause mortality (Los Angeles Veteran Study 1969, [60,61] Singh 1991[245])												
2	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/652 (27.9%)	188/652 (28.8%)	RR 0.96 (0.82 to 1.13)	12 fewer per 1000 (from 52 fewer to 37 more)	⊕⊕OO LOW	CRITICAL
CV mortality (Los Angeles Veteran Study 1969, [60,61] Singh 1991[,245])												
1	randomised trials	very serious[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	48/424 (11.3%)	70/422 (16.6%)	RR 0.68 (0.48 to 0.96)	53 fewer per 1000 (from 7 fewer to 86 fewer)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI (Los Angeles Veteran Study 1969 [60,61])												
2	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	37/651 (5.7%)	57/652 (8.7%)	RR 0.65 (0.44 to 0.96)	31 fewer per 1000 (from 3 fewer to 49 fewer)	⊕OOO VERY LOW	CRITICAL
Total stroke (Los Angeles Veteran Study 1969, [60,61] Singh 1991[,245])												
2	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	14/652 (2.1%)	25/652 (3.8%)	RR 0.56 (0.29 to 1.06)	17 fewer per 1000 (from 27 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL

[a]*Unclear allocation concealment, unclear if each arm had comparable care.*
[b]*Unclear allocation concealment and unclear if study arms received same care.*
[c]*The lower and upper limit of the confidence interval for the effect size cross 2 default MIDs (0.75 and 1.25, respectively), making the effect size uncertain.*
[d]*The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.*

Table 25: Clinical evidence profile: high polyunsaturated fat diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High polyunsaturated fat diet - Secondary prevention	Control	Relative (95% CI)	Absolute		
All-cause mortality (Research Committee MRC 1968,[2] Oslo Diet Heart Study 1966, Sydney Diet Heart Study 1978[217,281])												
3	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/626 (18.2%)	123/637 (19.3%)	RR 0.94 (0.75 to 1.18)	12 fewer per 1000 (from 48 fewer to 35 more)	⊕⊕OO LOW	CRITICAL
CV mortality (Oslo Diet Heart Study 1966,[144,145] Research Committee MRC 1968,[2] Rose 1965,[224] Sydney Diet Heart Study 1978[217,281])												
4	randomised trials	very serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/654 (23.7%)	104/663 (23.5%)	RR 1 (0.79 to 1.28)	0 fewer per 1000 (from 38 fewer to 47 more)	⊕⊕OO LOW	CRITICAL
Non-fatal MI (Oslo Diet Heart Study 1966,[144,145] Research Committee MRC 1968,[2] Rose 1965[224])												
2	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	serious[d]	none	26/227 (11.5%)	54/220 (24.5%)	RR 0.47 (0.3 to 0.72)	130 fewer per 1000 (from 69 fewer to 172 fewer)	⊕OOO VERY LOW	CRITICAL

[a]2/3 studies unclear allocation concealment, 1 study unclear missing data.
[b]3/4 studies unclear allocation concealment, 1/4 studies unclear missing data.
[c]2/2 studies unclear allocation concealment, 1/4 studies unclear missing data.
[d]The upper limit of the effect size crosses 1 default MID (0.75) making the effect size uncertain.

Table 26: Clinical evidence profile: low fat diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low fat diet	Usual diet - Secondary prevention	Relative (95% CI)	Absolute		
All-cause mortality (DART 1989,[41,42] Research Committee MRC 1965,[1] STARS 1992[272])												

3	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	no serious imprecision	none	132/1168 (11.3%)	140/1172 (11.9%)	RR 0.95 (0.76 to 1.19)	6 fewer per 1000 (from 29 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
CV mortality (Research Committee MRC 1965,[1] STARS 1992[272])												
2	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	18/150 (12%)	23/157 (14.6%)	RR 0.82 (0.46 to 1.45)	26 fewer per 1000 (from 79 fewer to 66 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI Research Committee MRC 1968,[2] Rose 1965,[224] Sydney Diet Heart Study 1978[217,281])												
3	randomised trials	very serious[d]	no serious inconsistency	very serious[b]	serious[e]	none	63/1168 (5.4%)	76/1172 (6.5%)	RR 0.85 (0.62 to 1.16)	10 fewer per 1000 (from 25 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Total stroke (STARS 1992[272])												
1	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/27 (0%)	1/28 (3.6%)	RR 0.35 (0.01 to 8.12)	23 fewer per 1000 (from 35 fewer to 254 more)	⊕OOO VERY LOW	CRITICAL

[a]3/3 studies unclear allocation concealment, 1 study unclear comparable care in study arms.
[b]1/3 studies intervention and control included indirect treatment populations.
[c]1/2 unclear allocation concealment.
[d]The lower and upper limit of the confidence intervals for the effect size cross 2 minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.
[e]The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.
[f]Unclear allocation concealment.

Table 27: Clinical evidence profile: increased fibre diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Increased fibre diet**	**Usual diet - Secondary prevention**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (DART 1989[41,42])												
1	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	serious[c]	none	123/1017 (12.1%)	101/1015 (9.9%)	RR 1.22 (0.95 to 1.56)	22 more per 1000 (from 5 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL

Non-fatal MI (DART 1989[41,42])												
1	randomised trials	very serious[a]	no serious inconsistency	very serious	very serious[d]	none	41/1017 (4%)	41/1015 (4%)	RR 1 (0.65 to 1.53)	0 fewer per 1000 (from 14 fewer to 21 more)	⊕OOO VERY LOW	I CRITICAL

[a]1/1 study unclear allocation concealment.
[b]Intervention and control included indirect treatment populations.
[c]The upper limit of the confidence interval for the effect size crosses the minimal important difference (1.25) making the effect size uncertain.
[d]The lower and upper limit of the confidence intervals for the effect size cross 2 minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.

Table 28: Clinical evidence profile: increased oily fish diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oily fish advice diet**	**Usual diet - Secondary prevention**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (DART 1989[41,42] DART 1989[41,42])												
2	randomised trials	serious[a]	no serious inconsistency	very serious[b]	serious[c]	none	161/1021 (15.8%)	134/1016 (13.2%)	RR 1.2 (0.97 to 1.48)	26 more per 1000 (from 4 fewer to 63 more)	⊕OOO VERY LOW	CRITICAL

[a]1/2 studies unclear allocation concealment.
[b]1/2 studies indirect intervention and control.
[c]The upper limit of the confidence intervals for the effect size cross the minimal important difference (1.25) making the effect size uncertain.

Table 29: Clinical evidence profile: increased fruit and vegetable diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Increased fruit and vegetable diet**	**Usual diet - Secondary prevention**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (DART 1989[41,42])												

2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	133/779 (15.8%)	109/764 (13.2%)	RR 1.2 (0.97 to 1.48)	26 more per 1000 (from 4 fewer to 63 more)	⊕OOO VERY LOW	CRITICAL

[a]*Unclear allocation concealment.*

[b]*The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.*

Table 30: Clinical evidence profile: Mediterranean diet versus control diet in primary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mediterranean diet	Usual diet - Primary prevention	Relative (95% CI)	Absolute		
All-cause mortality (PREDIMED 2013[88])												
1	randomised trials	serious[a]	no serious inconsistency	very serious[b]	no serious imprecision	none	234/4997 (4.7%)	228/4900 (4.7%)	RR 1.01 (0.84 to 1.2)	0 more per 1000 (from 7 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
CV mortality (PREDIMED 2013[88])												
1	randomised trials	serious[a]	no serious inconsistency[1]	very serious[b]	serious[c]	none	57/4997 (1.1%)	60/4900 (1.2%)	RR 0.93 (0.65 to 1.34)	1 fewer per 1000 (from 4 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI (PREDIMED 2013[88])												
1	randomised trials	serious[a]	no serious inconsistency	very serious[b]	serious[c]	none	68/4997 (1.4%)	76/4900 (1.6%)	RR 0.88 (0.63 to 1.21)	2 fewer per 1000 (from 6 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Total stroke (PREDIMED 2013[88])												
1	randomised trials	serious[a]	no serious inconsistency	very serious[b]	serious[4]	none	81/4997 (1.6%)	116/4900 (2.4%)	RR 0.68 (0.52 to 0.91)	8 fewer per 1000 (from 2 fewer to 11 fewer)	⊕OOO VERY LOW	CRITICAL

[a]*Unclear allocation concealment.*

[b]*Control arm advised to lower dietary fat and contained components of Mediterranean diet.*

[c]*The lower and upper limit of the confidence intervals for the effect size cross 2 minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.*

[d]*The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.*

Table 31: Clinical evidence profile: Mediterranean diet versus control diet in primary and secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mediterranean diet	Usual diet - Primary and secondary prevention	Relative (95% CI)	Absolute		
All-cause mortality (Indo-Mediterranean Diet Heart Study 2002[243])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	24/499 (4.8%)	38/501 (7.6%)	RR 0.63 (0.39 to 1.04)	28 fewer per 1000 (from 46 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI (Indo-Mediterranean Diet Heart Study 2002[243])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	21/499 (4.2%)	43/501 (8.6%)	RR 0.49 (0.3 to 0.81)	44 fewer per 1000 (from 16 fewer to 60 fewer)	⊕OOO VERY LOW	CRITICAL
Total stroke (Indo-Mediterranean Diet Heart Study 2002[243])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	7/499 (1.4%)	13/501 (2.6%)	RR 0.54 (0.22 to 1.34)	12 fewer per 1000 (from 20 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL

[a] *Unclear allocation concealment, unclear study arms received the same care.*
[b] *The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.*
[c] *The lower and upper limit of the confidence intervals for the effect size cross 2 minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.*

Table 32: Clinical evidence profile: Mediterranean diet versus control diet in secondary prevention populations

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mediterranean diet	Usual diet - Secondary prevention	Relative (95% CI)	Absolute		
All-cause mortality (Lyon Diet Heart study 1999[63-68,220])												

1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	14/302 (4.6%)	24/303 (7.9%)	RR 0.59 (0.31 to 1.11)	32 fewer per 1000 (from 55 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI (Lyon Diet Heart study 1999[63-68,220])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	8/302 (2.6%)	25/303 (8.3%)	RR 0.32 (0.15 to 0.7)	56 fewer per 1000 (from 25 fewer to 70 fewer)	⊕OOO VERY LOW	CRITICAL
Total stroke (Lyon Diet Heart study 1999[63-68,220])												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	0/302 (0%)	4/303 (1.3%)	RR 0.11 (0.01 to 2.06)	12 fewer per 1000 (from 13 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL

[a]*Unclear allocation concealment.*
[b]*The lower limit of the confidence interval for the effect size crosses the minimal important difference (0.75) making the effect size uncertain.*
[c]*The lower and upper limit of the confidence intervals for the effect size cross 2 minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.*

8.4 Economic evidence

Published literature

One economic evaluation was included that compared a Mediterranean diet with usual diet in adults with established CVD.[59] This is summarised in the economic evidence profile below (Table 33) and the economic evidence table in Appendix H.

No relevant economic evaluations were identified in adults without established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease, and no relevant economic evaluations were identified in adults with established CVD for dietary interventions other than a Mediterranean diet.

Two economic evaluations relating to this review question were identified but were excluded due to limited applicability or methodological limitations.[210,291] These are listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow diagram in Appendix E.

Table 33: Economic evidence profile: Mediterranean diet versus usual diet for secondary prevention of CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Dalziel 2006[59] (Australia)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis • Intervention: advice from dietitian to adopt a Mediterranean-type diet and supplied with rapeseed margarine • Effectiveness: Lyon Diet Heart Study[63-68,220] (France) • Cost year: 2003 (Australia) [(c)] • Time horizon: 10 years	−£135 [(d)]	0.40 QALYs gained	Mediterranean diet dominates usual diet (that is, it is cheaper and more effective) [(d)]	Sensitivity analyses were carried out on the base case results (including food costs) and showed ICERs varying from £198 to £3389 per QALY gained. Equivalent analyses excluding food costs would be expected to show that the Mediterranean diet dominates for all scenarios apart from doubling the number of dietitian consultations (for which the ICER would be around £228 per QALY gained).

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

(a) 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.

(b) 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.

(c) Converted using 2003 purchasing power parities.[204]

(d) Food costs were included in the base case results. The results presented here are for a sensitivity analysis which excluded food costs.

8.5 Evidence statements

Clinical

High polyunsaturated fat diet versus usual hospital diet, primary prevention populations

- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing all-cause mortality at 54 months, but the direction of the estimate of effect favoured usual diet (1 study, n=9057).
- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing stroke at 54 months, but the direction of the estimate of effect favoured high polyunsaturated fatty acids diet (1 study, n=9057).

Subgroup analysis: men

- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing all-cause mortality at 54 months, but the direction of the estimate of effect favoured usual diet (1 study, n=4393).
- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing stroke at 54 months, but the direction of the estimate of effect could favour either intervention (1 study, n=4393).

Subgroup analysis: women

- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing all-cause mortality at 54 months, but the direction of the estimate of effect favoured usual diet (1 study, n=4664).
- Very low quality evidence suggested that there may be no clinical difference between high polyunsaturated fatty acids diet and usual hospital diet at reducing stroke at 54 months, but the direction of the estimate of effect could favour either intervention (1 study, n=4664).

High polyunsaturated fat diet versus usual diet, mixed primary and secondary prevention populations

- Low quality evidence showed that there is be no clinical difference between high polyunsaturated fatty acids diet and usual diet at reducing all-cause mortality at 1 to 8 years (2 studies, n=1304).
- Very low quality evidence suggested that high polyunsaturated fatty acids diet is potentially more clinically effective when compared to usual diet at reducing CV mortality at 8 years (1 study, n=850), non-fatal MI at 1 to 8 years (2 studies, n=1304), and stroke at 1 to 8 years (2 studies, n=1304) at 1 to 7 years.

High polyunsaturated fat diet versus usual diet, secondary prevention populations

- Moderate quality evidence showed that there is be no clinical difference between high polyunsaturated fatty acids diet and usual diet at reducing all-cause mortality at 5 to 6 years (3 studies, n=1263).
- Low quality evidence showed that there is be no clinical difference between high polyunsaturated fatty acids diet and usual diet at reducing CV mortality at 2 to 6 years (4 studies, n=1317).
- Very low quality evidence suggested that high polyunsaturated fatty acids diet is potentially more clinically effective when compared to usual diet at reducing non-fat l MI at 2 to 6 years (2 studies, n=447).

Low fat diet versus usual diet, secondary prevention populations

- Very low quality evidence showed that there is be no clinical difference between low fat and usual diet at reducing all-cause mortality at 3 to 5 years (3 studies, n=2340).
- Very low quality evidence suggested that there may be no clinical difference between low fat and usual diet at reducing CV mortality at 3 to 5 years, but the direction of the estimate of effect could favour either intervention (2 studies, n=307).
- Very low quality evidence suggested that there may be no clinical difference between low fat and usual diet at reducing non-fatal MI at 2 to 5 years, but the direction of the estimate of effect favoured low fat diet (3 studies, n=2340).
- Very low quality evidence suggested that there may be no clinical difference between low fat and usual diet at reducing stroke at 3 years, but the direction of the estimate of effect could favour either intervention (1 study, n=55).

Increased fibre diet versus advice to eat a balanced diet, secondary prevention populations

- Very low quality evidence suggested that there may be no clinical difference between increased fibre and advice to eat a balanced diet at reducing all-cause mortality at 2 years, but the direction of the estimate of effect favoured usual diet (1 study, n=2032).
- Very low quality evidence suggested that there may be no clinical difference increased fibre and advice to eat a balanced diet at reducing non-fatal MI at 2 years, but the direction of the estimate of effect could favour either intervention (1 study, n=2032).

Increased oily fish diet versus usual advice to eat a balanced diet, secondary prevention population

- Very low quality evidence suggested that there may be no clinical difference between increased oily fish diet and advice to eat a balanced diet at reducing all-cause mortality at 2 years, but the direction of the estimate of effect favoured usual diet (2 studies, n=2037).

Increased fruit and vegetables diet versus advice to eat a balanced diet, secondary prevention populations

- Very low quality evidence suggested that there may be no clinical difference between Increased fruit and vegetables diet and advice to eat a balanced diet at reducing all-cause mortality at 2 years, but the direction of the estimate of effect could favoured usual diet (1 study, n=1543).

Mediterranean diet versus a control diet (low fat diet and some components of a Mediterranean diet (based on American Heart Association Step 1 diet)), primary prevention populations

- Very low quality evidence showed that there is be no clinical difference between Mediterranean diet with nuts and control diet at reducing all-cause mortality at 6 years, but the direction of the estimate of effect favoured usual diet (1 study, n=4904).
- Very low quality evidence showed that there is be no clinical difference between Mediterranean diet with olive oil and control diet at reducing all-cause mortality at 6 years, but the direction of the estimate of effect favoured Mediterranean diet with olive oil (1 study, n=4993).
- Very low quality evidence showed that there is be no clinical difference between Mediterranean diet with nuts and control diet at reducing non-fatal MI at 6 years, but the direction of the estimate of effect favoured Mediterranean diet with nuts (1 study, n=4904).
- Very low quality evidence showed that there is be no clinical difference between Mediterranean diet with olive oil and control diet at reducing non-fatal MI at 6 years, but the direction of the estimate of effect favoured Mediterranean diet with olive oil (1 study, n=4993).
- Very low quality evidence suggested that Mediterranean diet with nuts is potentially more clinically effective when compared with control diet at reducing stroke 6 years (1 study, n=4904).

- Very low quality evidence showed that there is be no clinical difference between Mediterranean diet with olive oil and control diet at reducing stroke 6 years, but the direction of the estimate of effect favoured Mediterranean diet with olive oil (1 study, n=4993).

Mediterranean diet versus a control diet based on the National Cholesterol Education Program in the step I diet mixed primary and secondary prevention populations

- Very low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to control diet at reducing all-cause mortality at 2 years (1 study, n=1000).
- Very low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to control diet at reducing CV mortality at 2 years (1 study, n=1000).
- Very low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to control diet at reducing stroke at 2 years, but the direction of the estimate of effect could favour either intervention (1 study, n=1000).

Mediterranean diet versus a prudent diet, secondary prevention populations

- Very low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to a prudent diet at reducing all-cause mortality at 46 months (1 study, n=605).
- Low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to a prudent diet at non-fatal MI at 46 months (1 study, n=605).
- Very low quality evidence suggested that Mediterranean diet is potentially more clinically effective when compared to a prudent diet at reducing stroke at 46 months, but the direction of the estimate of effect could favour either intervention (1 study, n=605).

Economic

- One cost–utility analysis found that in adults with established CVD a Mediterranean diet was dominant (less costly and more effective) compared to a usual diet for the secondary prevention of CVD. This analysis was assessed as partially applicable with potentially serious limitations.

8.6 Recommendations and link to evidence

Recommendations	**29. Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats. Further information and advice can be found at NHS Choices. [new 2014]** **30. Advise people at high risk of or with CVD to:** • **reduce their saturated fat intake.** • **increase their mono-unsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils and to use them in food preparation.** **Further information and advice on healthy cooking methods can be found at NHS Choices. [new 2014]** **31. Advise people at high risk of or with CVD to do all of the following:** • **choose wholegrain varieties of starchy food**

	• **reduce their intake of sugar and food products containing refined sugars including fructose** • **eat at least 5 portions of fruit and vegetables per day** • **eat at least 2 portions of fish per week, including a portion of oily fish** • **eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week.** **Further information and advice can be found at NHS Choices. [new 2014]** **32. Advise pregnant women to limit their oily fish to no more than 2 portions per week and to avoid marlin, shark and swordfish. Further information and advice on oily fish consumption can be found at NHS Choices. [new 2014]** **33. Take account of a person's individual circumstances – for example, drug therapy, comorbidities and other lifestyle modifications when giving dietary advice. [new 2014]** **34. Advise and support people at high risk of or with CVD to achieve a healthy diet in line with Behaviour change: the principles for effective interventions (NICE public health guidance 6). [new 2014]**
Relative values of different outcomes	All-cause mortality, CV, non-fatal MI, stroke or TIA, and quality of life were considered critical outcomes. Adverse events were considered relevant. The outcomes from RCTs included in the review protocol were supplemented by knowledge from observational and physiological studies and national policies. Outcomes specific to CV morbidity and mortality were included in the review but the GDG were aware of other potential benefits from healthy diets such as effect on risk of cancer.
Trade-off between clinical benefits and harms	The evidence from the clinical review was mixed. The GDG wished to use the review to provide more detail on dietary interventions and did not consider it would be adequate to overturn the general principles of a healthy diet. There was no evidence of benefit for all-cause mortality for any of the dietary interventions with the exception of potential benefit for the Mediterranean diet in a mixed primary and secondary prevention population (Singh 2002[243]) and in secondary prevention (Lyon Diet Heart Study 1999[63-68,220]). There was evidence of potential benefit for a high polyunsaturated fat diet for CV mortality in a mixed primary and secondary prevention study (Los Angeles Veteran Study 1969[60,61]), and for non-fatal MI in secondary prevention study (Research Committee MRC, 1968[2] Rose 1965[224]). A Mediterranean diet was of potential benefit for the outcome of non-fatal MI in a mixed primary prevention study (Singh 2002[243]) and a secondary prevention study (Lyon Diet Heart Study 1999[63-68,220]). No evidence of benefit was found for the following dietary interventions: low fat, increased fibre, increased oily fish and increased fruit and vegetables. No studies examined adverse events associated with dietary interventions. There was no evidence for the quality of life outcome. The GDG considered it unlikely that any of the diets recommended would cause significant clinical harm but noted that changes in diets may impose costs on people and that long term clinical benefit may appear less important to those on reduced

	budgets.
Economic considerations	One cost–utility analysis was identified relating to a Mediterranean diet.[59] This was based on the Lyon Diet Heart Study[63-68,220] and found that a Mediterranean diet was less costly and more effective compared to a usual diet in adults with established CVD. The costs of buying food are not included within the NHS and personal social services perspective, and so the only costs to be considered are those for providing information and of consultations with GPs or dietitians for advice and check-ups. These costs are relatively low unless consultations are very frequent, and therefore in general any dietary intervention which is clinically effective and to which individuals can adhere is likely to be cost effective and could be cost saving from an NHS and personal social services perspective. The GDG noted that any recommendation to change diets which imposes extra costs on people due to the substitution of more expensive foods for less expensive foods would be problematic to those with constrained disposable incomes, and so may be declined or not followed. Alternatively, adopting some more expensive dietary options may lead to additional changes in shopping habits to save money elsewhere, which may lead to unpredictable changes to diet and hence also to health outcomes. Changes to diet which are cost neutral or cost saving on overall food and drink spending are therefore preferable.
Quality of evidence	The majority of studies were underpowered for all-cause mortality and CV outcomes. The data was of low or very low quality. The GDG noted that as 9 out of 14 studies were conducted before 1990 they were not applicable to current practice because of profound changes in lifestyles such as diet and alcohol consumption, and because statins were not available before 1990. Only 3 studies reported on usage of lipid-lowering therapy (Lyon Diet Heart Study 1999[63-68,220]: 30%, PREDIMED 2013[88]: 45%, Singh 2002[243]: 4%). The GDG were aware that in some studies the control groups were given general advice to improve their diet, while in others more specific advice was given. Some studies only cited 'control diet' with no further information. The GDG noted that one study's recruitment was interrupted for a year and that in the second phase of the study there was a subsequent sub-randomisation of the fish advice group to receive either fish advice or capsules (DART 2 2003[40]). The GDG were made aware that concerns have been raised[151,247] of suspected fraud relating to the Indo-Mediterranean Diet Heart Study published in the Lancet (Singh 2002[243]). As a result, the Lancet issued an expression of concern in 2005[120] but were unable to justify retracting the paper. It is hence still included in the review, however the results were considered with caution. The GDG noted that concerns have also been published[275] regarding another trial by the same author (Singh 1991[245]) included in this review.
Other considerations	The GDG were joined by a co-opted Public health specialist and CVD dietitian to inform the recommendations on diet. The GDG reviewed the original guideline recommendations. They considered that the recent evidence did not result in a major change to advice but that the wording could be improved to make the recommendations more useful for professionals and for patients. The original recommendations were informed by observational studies (epidemiological cohorts), government policy, and the limited RCT evidence. The GDG considered it was important to emphasise that advice should take account of dietary effects on overall health, not just its effects on lipid modification. The GDG considered that reference to NICE public health guidance on Behaviour modification should be an important part of advice giving on dietary changes. Studies on increased polyunsaturated fats diets varied considerably in their individual components and ratio of polyunsaturated versus monounsaturated fat was not reported. The GDG noted that a reduction in the consumption of animal

	sources of saturated fats also leads to a decrease in the consumption of monounsaturated fats and this need to be replaced. The GDG considered it important to provide examples of polyunsaturated and monounsaturated fats in the recommendations, and that people should be advised to have an adequate amount of unsaturated fats. The most up to date study from Spain that examined 'Mediterranean diet' was difficult to interpret because the control group was advised to reduce their fat intake and to follow some of the components of the Mediterranean diet (PREDIMED 2013[88]). However the GDG noted that for Mediterranean diet plus nuts and Mediterranean diet plus olive oil versus control diet, the adjusted hazard ratios for the primary composite outcome of reduction in CV events were 0.72 (0.54 to 0.96) and 0.70 (0.54 to 0.92), respectively The French 'Mediterranean diet' study (Lyon Diet Heart Study 1999[63-68,220] may be confounded given the control group may have been following a diet that is atypical when compared to the standard UK diet and other countries' diet. The GDG noted that the control group of the Lyon Diet Heart study[63-68,220] consumed a greater quantity of linoleic acid which is found in sunflower and soy oil, while the intervention group's diet was high in alpha-linolenic acid which is found in olive oil and rapeseed oil.[63] Therefore the GDG decided to preferentially recommend the consumption of olive oil and rapeseed oil. Several studies used the term 'Mediterranean diet' but the GDG noted that there may be uncertainty as to what constitutes a Mediterranean diet. The 'Mediterranean diet' intervention in an Indian study (Singh 2002) is different compared with Spanish and French studies. The co-optee informed the GDG that people can understand the term 'Mediterranean' diet to apply to foods they commonly associate with Mediterranean countries such as pasta and pizza. The GDG concluded that recommendations should avoid using this dietary description as it is non-specific. The GDG included in the recommendations thenational advice that pregnant women should be advised to avoid marlin, shark and swordfish in addition to limiting their oily fish consumption. The GDG considered dietary intervention advice should be given in consideration of other medical interventions, comorbidities and lifestyle modification.

9 Lifestyle modifications for the primary and secondary prevention of CVD [2008]

9.1 Introduction – lifestyle modification for the primary and secondary prevention of CVD

There is a substantive and consistent body of epidemiological, physiological and observational evidence demonstrating that changes in diet modify blood lipids and other risk factors and that these changes are associated with reductions in morbidity and mortality from CVD. Similarly epidemiological, physiological and observational evidence supports the association between cardiovascular health and levels of moderate or greater physical activity and associates a sedentary lifestyle with increased cardiovascular risk.

It is difficult to design, fund or organise randomised trials sufficiently large and rigorous that can yield evidence for the effect of diet, physical activity, smoking cessation or multifactorial lifestyle interventions on cardiovascular events. The observational literature on diet, dietary modification and physical activity provides a large body of evidence that has been periodically reviewed for major national initiatives. It is beyond the resources of this guideline to attempt such a review and we have referenced national reports and systematic reviews and cross referred to appropriate national advice.

To maintain consistency of reporting across both pharmacological and lifestyle interventions, we have limited formal searches for evidence to randomised trials with outcomes that include cardiovascular events. Such studies are few and we are acutely aware that this limited trial evidence does not adequately reflect either the strength or breadth of evidence that can be derived from epidemiology and other observational work.

2008

The 1976 Doll and Peto study based on 20 years observation of smoking among British doctors[74] remains a seminal descriptor of a clearly defined and modifiable risk factor. The 50 year prospective follow up study (1951 to 2001) showed that men born between 1900 and 1930 who continued to smoke cigarettes died on average about 10 years younger than those who were lifelong non-smokers, while those who stopped at around 60, 50, 40 or 30 gained, respectively, on average 3, 6, 9, or 10 years of life expectancy compared with those who continued.[74] For men born between 1900 and 1930, the absolute difference between cigarette smokers and non-smokers in the probability of death in middle age increased from 18% (42% versus 24%, a twofold death rate ratio) for those born in the first decade of the century, and for those born in the second decade the probability of death increased to 28% (43% versus 15%, a threefold death rate ratio)[74] The authors concluded that among men born around 1920 prolonged cigarette smoking from an early adult age tripled age specific mortality rates, but at age 50 halved the hazard and at age 30 avoided almost all of it.[74]

There is extensive and robust trial evidence that smoking cessation programmes are effective in reducing smoking[282,283] However, no randomised controlled trials with cardiovascular outcomes resulting from smoking cessation have ever been conducted, though there is clear evidence from observational studies that smoking cessation is associated with 40% lower morbidity and mortality.[15] Differences in the prevalence of smoking between the higher and lower social classes has been estimated to account for over half the difference in the risk of premature death faced by these groups.[127,128] Consumption of tobacco in forms other than smoking should also be noted. High consumption of alcohol is also associated with substantially increased rates of coronary heart disease and all-cause mortality.[84,85]

For secondary prevention most trial evidence relates to patients following myocardial infarction and that evidence is covered in the NICE guideline: 'Myocardial infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction', CG48 (2007) http://guidance.nice.org.uk/CG48. Trial literature is almost completely absent for lifestyle interventions in secondary prevention of stroke and peripheral arterial disease.

9.2 Regular physical activity

9.2.1 Evidence Statements for physical activity

No randomised controlled trials were identified in people at high risk of CVD that compared regular physical activity with sedentary lifestyle for the outcomes mortality or morbidity.
Two studies found that programmes to increase physical activities were cost effective compared to no exercise programmes in improving outcomes for people at risk of CVD.
No randomised controlled trials were identified in patients with angina, peripheral arterial disease or following stroke that compared regular physical activity with sedentary lifestyle for the outcomes of mortality or morbidity.
In selected patients after an MI, randomisation to an exercise prescription programme reduced the risk of death from MI after 3 years, but not all cause or cardiovascular mortality.
In selected patients after an MI, exercise performed at a level sufficient to increase physical work reduced all-cause mortality and cardiovascular mortality in long term follow up.
One small randomised controlled trial in patients with stable intermittent claudication showed that physical training classes were not associated with a reduction in total cholesterol or triglyceride levels compared with usual care.
Two cost effectiveness studies concluded that exercise programmes are cost effective compared to no exercise programme in patients with CHD.

2008

9.2.2 Clinical effectiveness of regular physical activity for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of regular physical activity versus sedentary lifestyle for the outcomes of all-cause mortality, cardiovascular mortality or cardiovascular morbidity.

9.2.3 Cost effectiveness of regular physical activity for the primary prevention of CVD

Two studies were found which addressed this question, one Canadian[148] and one American.[156] None of the studies were done in the UK.

Study[156] was a cost utility analysis which used effectiveness data from the Framingham study. It was not clear as to the sources of the utility data they used in their decision model however it did use appropriate methodology. The authors did not provide resource use and quantities separately which makes it difficult to reproduce their work.

The authors reported that exercise resulted in 529.8 discounted QALYs over the 30 year follow up. Cost/QALY gained was $1395/QALY. A range of univariate sensitivity analyses were done, and the model was robust to all changes in assumptions that were tested.

The second study[148] was a cost effectiveness which used effectiveness data from a number of different studies published between 1980 and 1999. The authors were very detailed in their reporting and references were provided. Resource use and quantities were provided separately.

The authors reported results separately for men and women and stratified results into three age groups. The results showed that exercise, especially unsupervised exercise was a cost effective intervention compared to no exercise. The benefits were more for younger men and less in the elderly man and women. The cost per life year gained ranged between $645/LYG for the 35-54year age group in unsupervised men to $30704 in the 65-74 year age group attending supervised sessions. For women the incremental cost effectiveness ratios for women ranged between $4915 to $87166 respectively.

In conclusion, a programme to increase physical activity compared to no programme is cost effective in improving outcomes for people at risk of CVD. The results from the two studies showed that younger men benefit more from such programmes than older men and women. Results also showed that unsupervised activity is more cost effective than supervised classes. This however depended on the assumption that there is almost 100% adherence to the exercise programme.

9.2.4 Evidence into recommendations

Due to the lack of clinical outcome data, it was decided by the GDG that recommendations would be made based on those of the following documents:

- The Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health'.[72]
- The NICE public health intervention guidance no. 2 ‘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’.[180]
- The Joint British Societies' guidelines on prevention of CVD in clinical practice.[280,281]

2008

These guidelines recommend that thirty minutes of at least moderate intensity activity should be taken per day, at least five days a week. The chief medical officer’s report (ref) describes what is meant by moderate intensity activity: A person who is doing moderate intensity activity will usually experience:

- An increase in breathing rate
- An increase in heart rate, to the level where the pulse can be felt, and
- A feeling of increased warmth, possibly accompanied by sweating on hot or humid days.

Also, a bout of moderate intensity activity can be continued for many minutes without a feeling of exhaustion.

The typical activity pattern of a moderately active person would include doing one or more of the following:

- Regular active commuting on foot or by bicycle
- Regular work related physical tasks
- Regular household and garden activities
- Regular active recreation or social sport at moderate intensity.

Examples of the intensities and energy expenditures for common types of physical activity are given in Table 34.

Table 34: Intensities and energy expenditures for common types of physical activity

Activity	Intensity	Intensity (METS)	Energy expenditure (Kcal equivalent, for a person of 60kg doing the activity for 30n minutes)
Ironing	Light	2.3	69
Cleaning and dusting	Light	2.5	75
Walking – strolling, 2mph	Light	2.5	75
Painting/decorating	Moderate	3	90
Walking – 3mph	Moderate	3.3	99
Hoovering	Moderate	3.5	105
Golf – walking, pulling clubs	Moderate	4.3	129
Badminton – social	Moderate	4.5	135
Tennis – doubles	Moderate	5	150
Walking – brisk, 4mph	Moderate	5	150
Mowing lawn – walking, using power-mower	Moderate	5.5	165
Cycling – 10-12mph	Moderate	6	180
Aerobic dancing	Vigorous	6.5	195
Cycling – 12 -14mph	Vigorous	8	240
Swimming – slow crawl, 50 yards per-minute	Vigorous	8	240
Tennis – singles	Vigorous	8	240
Running – 6mph (10minutes/mile)	Vigorous	10	300
Running – 7mph (8.5minutes/mile)	Vigorous	11.5	345
Running – 8mph (7.5 minutes/mile)	Vigorous	13.5	405

MET = Metabolic equivalent
1 MET = A persons metabolic rate (rate of energy expenditure) when at rest
2 METs = A doubling of the resting metabolic rate
Adapted from the Chief Medical Officers (2004). Found at: www.dh.gov.uk

2008

The Chief Medical Officer's report also provides useful information on the potential risks associated with physical activity. It stresses that the risks associated with taking part in physical activity at levels that promote health are low and that the health benefits far outweigh the risks. The report states that the greatest risks in terms of sustaining sports injuries are faced by:

- People who take part in vigorous sports and exercise
- People to do 'excessive' amounts of exercise, and
- People with existing musculoskeletal disease or at high risk of disease.

In relation to cardiovascular risk, the report states that 'extremely rarely, inactive and unfit individuals who start doing vigorous physical activity may face increased cardiovascular risks'. In addition, it states that vigorous levels of activity may increase the risk of heart attack, although this increased risk appears to only apply to men with high blood pressure and is largely limited to people who do not exercise regularly.

9.2.5 Clinical effectiveness of regular physical activity for primary and secondary prevention of CVD

No randomised controlled trials were identified in patients with a history of angina alone, stroke, or peripheral arterial disease that examined the effect of regular physical activity versus a sedentary lifestyle for the outcomes of all-cause mortality, cardiovascular mortality or cardiovascular morbidity.

One randomised controlled trial was identified on the effectiveness of regular physical activity versus sedentary lifestyle to modify lipid profiles in patients with a history of stable intermittent claudication for at least six months.[99].The trial recruited men and women from a regional cohort of 400 to 500 people. A total of 264 participants were randomised to one of three groups:

1. Usual care
2. Physical training classes (a program of 3 X 30 minute sessions of specific walking training per week for the first six months, supervised by a physiotherapist. From 6 months to 1 year, 2 sessions per week were offered)
3. Invasive treatment (endovascular or open surgical procedure).

Participants were then followed up for 1 year. Physical training classes did not confer any benefit over usual care for the primary outcome of maximum exercise power in Watts or for the secondary physiological endpoints. Total cholesterol and triglycerides were measured at randomisation and at 1 year and there were no differences between the physical training class and usual care groups. In addition, no difference in the number of deaths was seen between groups however, this was not a pre-specified outcome measure.

Due to the lack of clinical outcome data in this trial, it was decided by the GDG to consider evidence used in the NICE guidance: 'Myocardial infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction', CG48.[175]

2008

Two studies were identified which examined the impact of regular physical activity to improve outcome in patients with a prior MI. The first study was a randomised controlled trial in 651 men, aged 35 to 64 years with a documented MI greater than or equal to 8 weeks but less than 3 years before recruitment conducted between 1976 and 1979.[192]

The exercise intervention was an individualised exercise prescription based on the patient's ECG-monitored treadmill multistage graded test (MSET). An exercise target heart rate guided the prescription and was determined as 85% of the peak rate achieved on the MSET. This group performed brisk physical activity in the laboratory for 8 weeks (1 hour per day, 3 times per week). After 8 weeks, participants exercised in a gymnasium or swimming pool (15 minutes cardiac exercise followed by 25 minutes of recreational games). Participants were encouraged to attend 3 sessions per week. Patients in the control group were told to maintain their normal routine but not to participate in any regular exercise.

At the 3 year follow up, randomisation to the exercise prescription programme was found to be associated with a reduction in death from MI (RR 0.13, 95% CI 0.02 to 0.78) compared with control. The exercise intervention was not associated with a reduction in all-cause mortality (RR 0.63, 95% CI 0.32 to 1.15) or cardiovascular mortality (RR 0.71, 95% CI 0.34 to 1.33) compared with control. The authors noted that by the end of the trial 23% of the treatment group had stopped attending exercise sessions, whereas 31% of the control group reported that they were exercising regularly.[192] A secondary analysis of this data[75] presented age- adjusted risk ratios and it was found that at the 3 year follow up point, the exercise intervention was associated with a reduction in all-cause mortality (0.86, 95% CI 0.76 to 0.98) but not CVD mortality (0.87, 95% CI 0.74 to 1.02) compared with control.

After 3 years of the trial, the patients were followed up for 5, 10, 15 and 19 years examining all cause mortality and cardiovascular mortality. The results of this follow - up were published in the second study[75] which was a secondary analysis of the first study. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for all cause mortality were 0.91 (95% CI 0.82 to1.00), 0.88 (95% CI 0.83 to 0.95), 0.89 (95% CI 0.84 to 0.95) and 0.92 (95% CI 0.87 to 0.97), respectively for the exercise prescription programme compared with control. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for CVD mortality were 0.91 (95% CI 0.81 to 1.03), 0.89 (95% CI 0.82 to 0.96), 0.89 (95% CI 0.82 to 0.96) and 0.93 (95% CI 0.87 to 0.99), respectively for the exercise prescription programme compared with control.

Thus, improvement in physical work capacity resulted in consistent survival benefits throughout the full 19 years. The authors concluded that exercise performed at a level sufficient to increase physical work capacity may have long-term survival benefits in MI survivors.

9.2.6 Evidence into recommendations

It was decided by the GDG that recommendations would be made based on those of the Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health'[72] and the NICE public health intervention guidance no. 2 ‘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’[180], and the Joint British societies' guidelines on prevention of CVD in clinical practice.[280,281]

Please refer to section on lifestyle for the primary prevention of CVD for further details of the Chief Medical Officer's report and see the full report at www.dh.gov.uk.

2008

9.3 Combined cardioprotective dietary advice and regular physical activity (primary prevention of CVD)

9.3.1 Evidence statements for combined cardioprotective dietary advice and regular physical activity

No randomised controlled trials were identified in people at high risk of CVD that compared combined cardioprotective dietary advice and regular physical activity with usual lifestyle for the outcomes mortality or morbidity.
One randomised controlled trial in people at high risk of CVD found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and triglycerides and an increase in HDL cholesterol levels compared with control. A second randomised controlled trial found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and LDL cholesterol compared with usual diet. A third randomised controlled trial found that a combination of diet and aerobic exercise was not associated with a change in lipid levels compared with control.

9.3.2 Clinical effectiveness of combined cardioprotective dietary advice and regular physical activity for the primary prevention of CVD

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of dietary advice versus usual diet and / or regular physical activity versus sedentary lifestyle for the outcomes of all-cause mortality, cardiovascular mortality or cardiovascular morbidity.

Three randomised controlled trials were identified which examined the effectiveness of diet, regular physical activity and the combination of both interventions to improve serum lipid level profiles in people with elevated CVD risk factors.[19,110,248]

The first study was a randomised controlled trial of six months duration in 158 healthy men aged 35 to 60 years with moderately elevated CVD risk factors.[110] Participants were randomised to one of three intervention groups or to the control group (usual lifestyle). The first intervention was diet whereby participants were given verbal and written dietary advice that total fat consumption should comprise no more than 30% of energy intake, saturated fat no more than 10% of energy, cholesterol consumption should be less than 300 mg/day, polyunsaturated fat up to 10% of energy, monounsaturated fat 10-15% energy, carbohydrates (mainly complex) 50-60% energy and protein 10-20% energy.

The second intervention was physical activity; participants were given verbal and written advice to take regular physical activity of an aerobic type 2-3 times per week for 30-45 minutes at 60-80% maximum heart rate.

The third intervention was a combination of diet and physical activity. The control group was told to continue with the diet and lifestyle as prior to joining the study.

After six months, lipid levels were measured and no significant differences were found in total cholesterol, LDL cholesterol or HDL cholesterol for any of the intervention groups compared to control.

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The second study was a randomised controlled trial[19,20] of one year duration in 198 men and 21 women aged 41-50. Participants who each had several coronary risk factors were recruited in Oslo and were then randomised to one of three intervention groups or to the control group. The dietary intervention consisted of counselling to reduce intake of saturated fat and cholesterol and to consume more fish. Energy restriction advice was given to those overweight.

For the physical activity intervention, participants attended aerobic exercise sessions 3 times per week for one hour where they exercised at 60-80% of their peak heart rate in supervised classes of 14 to 20 people.

The third intervention group was a combination of diet and physical activity as already described. The control group was told not to change their lifestyle during the trial but as all the other participants they were advised against smoking.

After one year, no significant differences in total, LDL or HDL cholesterol were observed for the diet only or physical activity only interventions compared to control. For the combined diet and physical activity intervention, a significant decrease in total cholesterol and a significant increase in HDL cholesterol were observed compared to control. In addition, triglycerides were found to be significantly reduced in all three intervention groups compared to control.

The final randomised controlled trial[248] was of one year duration and included 197 men and 180 postmenopausal women. Women were 45 to 64 years of age, had HDL cholesterol levels < 1.55 mmol/l, and LDL cholesterol levels between 3.23 and 5.42 mmol/l. Men were 30 to 64 years of age, had HDL cholesterol levels < 1.14 mmol/l, and LDL cholesterol levels between 3.23 and 4.90 mmol/l.

Participants were randomised to one of three intervention groups or to the control group. The first intervention was diet where participants were advised to follow the National Cholesterol Education Program (NCEP) Step 2 diet: total fat less than 30% of energy intake, saturated fat less than 7% of energy and cholesterol less than 200 mg per day.

The second intervention was aerobic exercise: participants attended 6 weeks of supervised 1 hour sessions, 3 times per week (held separately for groups 2 and 3). For the remaining 7 to 8 months of the trial, they could attend supervised classes and / or undertake home-based activities with the goal of engaging in aerobic activity equivalent to at least 16km of brisk walking or jogging each week.

The control group was asked to maintain their usual diet and exercise habits.

After one year, for both men and postmenopausal women, significant decreases in total and LDL cholesterol levels were observed in the diet plus physical activity intervention group compared to control.

In addition, one systematic review was identified that assessed the effectiveness of multiple risk factor interventions which included smoking cessation, physical activity and dietary advice with or without pharmacological intervention on a number of outcomes including all cause and CHD mortality.[77,78] A total of 39 randomised controlled trials were identified in adults of ≥ 40 years of age from general populations, workforce populations and high risk groups. Ten of these trials reported clinical event data and a meta-analysis of these ten trials found that multiple risk factor interventions were not associated with a reduction in total or coronary heart disease (CHD) mortality.

The conclusion of the review was that 'The pooled effects suggest multiple risk factor intervention has no effect on mortality. However, a small but potentially important benefit of treatment (about a 10% reduction in CHD mortality) may have been missed. Risk factor changes were relatively modest, were related to the amount of pharmacological treatment used, and in some cases may have been over-estimated because of regression to the mean effects, lack of intention to treat analysis, habituation to blood pressure measurement, and use of self-reports on smoking.'

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9.3.3 Evidence into recommendations

Due to the lack of evidence on the effectiveness of combined approaches, it was decided by the GDG that cardioprotective dietary advice and regular physical activity interventions would be considered separately.

9.3.4 Cost effectiveness of combined cardioprotective dietary advice and regular physical activity for the primary prevention of CVD

There were no cost effectiveness studies found surrounding the use of combined dietary advice and regular physical activity in the prevention of CVD.

9.4 Alcohol

Alcohol consumption for men should be limited to up 3 to 4 units a day, and for women alcohol should be limited to up to 2 to 3 units of alcohol a day. People should avoid binge drinking. Further information can be found on the Foods Standards Agency website www.eatwell.gov/healthdiet/.

9.5 Weight management

For guidance in weight management in people at high risk of CVD refer to the NICE guideline:

- Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children CG43[181]

9.6 Smoking cessation

For guidance on smoking cessation refer to the NICE Technology appraisals and guidance on public health interventions:

- Smoking cessation - bupropion and nicotine replacement therapy. The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation TA039.[178]
- Brief interventions and referral for smoking cessation in primary care and other settings PHI001.[179]
- Varenicline for smoking cessation. NICE technology appraisal guidance 123.[184]
- 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.[186]

9.7 Recommendations

9.7.1 Physical activity

Recommendations	**35. 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]** **36. Advise people to do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). [new 2014]** **37. 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]** **38. Advice about physical activity should take into account the person's needs, preferences and circumstances. Agree goals and provide the person with written information about the benefits of activity and local opportunities to be active, in line with Four commonly used methods to**

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	increase physical activity (NICE public health guidance 2). [2008]

9.7.2 Combined interventions (diet and physical activity)

Recommendation	**39. Give advice on diet and physical activity in line with national recommendations (see NHS Choices). [2008]**

9.7.3 Weight management

Recommendation	**40. Offer people at high risk of or with CVD who are overweight or obese appropriate advice and support to work towards achieving and maintaining a healthy weight, in line with Obesity (NICE clinical guideline 43). [2008]**

9.7.4 Alcohol consumption

Recommendation	**41. Be aware that men should not regularly drink more than 3–4 units a day and women should not regularly drink more than 2–3 units a day. People should avoid binge drinking. Further information can be found at NHS Choices. [2008]**

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9.7.5 Smoking cessation

Recommendations	**42. Advise all people who smoke to stop, in line with Smoking cessation services (NICE public health guidance 10). [2008]** **43. Offer people who want to stop smoking support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services). [2008]** **44. If a person is unable or unwilling to accept a referral to an intensive support service, offer them pharmacotherapy in line with Smoking cessation services (NICE public health guidance 10) and Varenicline for smoking cessation (NICE technology appraisal guidance 123). [2008]**

10 Plant stanols and sterols

10.1 Introduction

Plants synthesise sterols related to cholesterol. These phytosterols (including sitosterol, campesterol and sitostanol) are absorbed with dietary cholesterol and have been used as markers of cholesterol uptake[109,109] and as CVD risk factors in their own right. Sitosterol and sitostanol can interfere with intestinal cholesterol uptake when taken at high doses and modify enterocyte lipid metabolism. Both these plant sterols have been incorporated into dietary supplements ('nutriceuticals') that reduce LDL cholesterol in a dose-dependent manner.[100,138] They can also be added to food. Given the wide availability of these products, there is a need to review the evidence for their potential clinical effectiveness in preventing CVD.

10.2 Review question: 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 (primary prevention) and with established CVD (secondary prevention)?

For full details see review protocol in Appendix C.

Table 35: PICO characteristics of review question

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	• Phytosterol-enriched food (report statin usage as given in RCT baseline characteristics for each arm) or supplements
Comparison	• Placebo
Outcomes	7. All-cause mortality 8. CV mortality 9. Non-fatal MI 10. Stroke 11. Quality of life
Study design	RCTs, SRs of RCTs

10.3 Clinical evidence

No relevant clinical studies were identified that compared phytosterol-enriched foods or supplements with placebo and had relevant outcomes.

10.4 Economic evidence

Published literature

No relevant economic evaluations were identified that compared foods enriched with phytosterols with placebo in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease.

Four economic evaluations relating to this review question were identified but were excluded due to limited applicability or methodological limitations.[89,158,208] These are listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow diagram in Appendix E.

10.5 Evidence statements

Clinical

- No relevant clinical studies were identified.

Economic

- No relevant economic evaluations were identified.

10.6 Recommendations and link to evidence

Recommendations	**45. Do not advise any of the following to take plant stanols or sterols for the prevention of CVD:** • **people who are being treated for primary prevention** • **people who are being treated for secondary prevention** • **people with CKD** • **people with type 1 diabetes** • **people with type 2 diabetes. [new 2014]**
Relative values of different outcomes	Critical outcomes were all-cause mortality, CV mortality, non-fatal MI, stroke and quality of life.
Trade-off between clinical benefits and harms	No benefit was found for CV outcomes.
Economic considerations	No sufficiently relevant economic evidence was identified. If the use of foods enriched with phytosterols or -stanols is clinically effective, then it would be likely to be cost saving from an NHS and personal social services perspective as the cost of the enriched food or supplement is borne by the patient. However, the clinical review found no evidence regarding the effectiveness of this intervention in reducing CV events. It is hence impossible to say whether the intervention is cost effective. The GDG noted that any recommendation to people to use stanol or sterol supplementation would impose additional costs on the individual. As these costs would have to be paid for from within an unchanged personal disposable income, this may lead to changes in the individual's other shopping choices, which could

	impact upon the balance and healthiness of the individual or family's diet as a whole.
Quality of evidence	No evidence was found.
Other considerations	The GDG recognised that many people are reluctant to take drugs. People are also encouraged to reduce CV risk by lifestyle measure and this includes alterations to diet and weight. As part of this strategy plant stanols and sterol products are bought and consumed by people at all levels of CVD risk. The GDG considered that evidence for reduction of CVD outcomes was necessary in order for healthcare professionals to be able to advise people to use plant stanol and sterol supplements. They did not accept that an effect on surrogate outcomes was appropriate to allow recommendation for this class. The GDG discussed the use of supplementation with plant stanols and sterols when discussing the evidence for the effect of diet on CV outcomes (see Chapter 8). It was agreed that advice should emphasise appropriate diet rather than supplementation.

11 Statins for the primary and secondary prevention of CVD

11.1 Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) were discovered in 1971 as part of studies to find fungi, and isolate the compounds they produced, which would inhibit the synthesis of cholesterol.[250] Statins were first used in humans in 1980. A wide variety of statins have since been developed. The efficacy of statins and adverse events associated with statin therapy have been assessed in a variety of populations, including people with hypercholesterolaemia, people being treated for primary and secondary prevention of CVD, including people with coronary heart disease (CHD), stroke, diabetes and renal disease. Though few direct comparison studies have been performed, the similarity of these trial designs has allowed meta-analyses to be conducted of the safety and efficacy of statins across their dose ranges. The primary outcome in these studies are the changes in lipid sub-fractions, allied with documentation of clinical adverse events (such as myalgia and rhabdomyolysis) and measurement of biomarkers of potential statin toxicity, including the incidence of raised liver transaminases (greater than 3 times the upper limit of normal), and elevations in creatine kinase (greater than 10 times the upper limit of normal).

The first randomised trial of statins with clinical outcomes was started in 1989 and specified total mortality as an outcome. The Scandinavian Simvastatin Survival Study in 1994[5] proved a landmark study, demonstrating the benefits of statin therapy in patients with established CVD and led to a whole series of statin trials in both primary and secondary prevention populations, patients with strokes, diabetes, renal disease and chronic heart failure. The results of these studies have been combined into an individual patient-based meta-analysis of over 90,000 and 100,000 patients- the Cholesterol Treatment Trialists' Collaboration.[12,26,169]

Statins are recognised as the first choice lipid modification therapy to reduce CVD events. Statin therapy was first appraised by NICE as part of the technology appraisal TA94 ('Statins for the prevention of cardiovascular events' 2006). This was followed by clinical guidelines which made specific recommendations about use of statins in people with and without diabetes. The scope for this update includes the use of statins in people for primary prevention, secondary prevention, type 1 and type 2 diabetes and people with CKD. The evidence review and the health economic models were updated to include changes to the evidence base, clinical practice and NHS costs since the publication of the previous guideline.

Statins are grouped in this guideline as seen in Table 36. This grouping was agreed by GDG consensus, informed by analyses in the literature. This grouping is discussed further in Section 11.8.

Table 36: Grouping of statins

	% reduction in low-density lipoprotein cholesterol				
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	10%[1]	15%[1]	21%[2]	27%[2]	33%[3]
Pravastatin	15%[1]	20%[2]	24%[2]	29%[2]	33%[1]
Simvastatin	23%[1]	27%[2]	32%[3]	37%[3]	42%[4*]
Atorvastatin	31%[1]	37%[3]	43%[4]	49%[4]	55%[4]
Rosuvastatin	38%[3]	43%[4]	48%[4]	53%[4]	58%[1]

1 Not available in the UK.

2 20%–30%: low intensity.
3 31%–40%: medium intensity.
4 Above 40%: high intensity.
** Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80-mg dose 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.*

The information used to make the table is from Law 2003 [141,141](BMJ 2003;326:1423).

11.2 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)?

For full details see review protocol in Appendix C.

Table 37: PICO characteristics of review question

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: • Atorvastatin • Fluvastatin • Pravastatin • Rosuvastatin • Simvastatin
Comparison[(a)]	1. Low intensity group[(b)] (pravastatin 10–40 mg or equivalent) 2. Medium intensity group[(c)] (simvastatin 40 mg or equivalent) 3. High intensity group[(d)] (atorvastatin 80 mg or equivalent) 4. Placebo
Outcomes	• All-cause mortality • CV mortality • Non-fatal MI • Stroke • Quality of life • Adverse event: Rhabdomyolysis (CK more than 10 times the upper limit of normal) • Adverse event: Myalgia • Adverse event: Liver (transaminases more than 3 times the upper limit of normal) • Adverse event: New-onset diabetes • LDL-cholesterol reduction
Study design	RCTs and SRs of RCTs; minimum follow up: 1 year

(a) Source for grouping of statins according to intensity of LDL-cholesterol reduction: Law 2003[141]
(b) Low intensity (LDL-cholesterol reduction of 20%–30%): fluvastatin 20 mg, fluvastatin 40 mg, pravastatin 5 mg, pravastatin 10 mg, pravastatin 20 mg, pravastatin 40 mg, simvastatin 10 mg
(c) Medium intensity (LDL-cholesterol reduction of 31%–40%): atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg, simvastatin 20 mg, simvastatin 40 mg

(d) High intensity (greater than 40% LDL-cholesterol reduction): atorvastatin 20 mg, atorvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 10 mg, rosuvastatin 20 mg, rosuvastatin 40 mg, simvastatin 80 mg.

11.3 Clinical evidence (statins versus placebo and head-to-head comparisons of statins)

Statins were grouped according to intensity of LDL-cholesterol reduction as detailed in Table 2. Effectiveness was analysed by group. The statin grouping was based on GDG consensus informed by clinical consensus and an analysis of LDL-cholesterol reduction from 164 short-term trials (minimum duration 2 weeks)[141]

Table 38: Statin intensity according to individual drug and dose

Intensity	Statin and dose	LDL-cholesterol reduction (%)
Low intensity	• Fluvastatin 20 mg • Fluvastatin 40 mg • Pravastatin 5 mg • Pravastatin 10 mg • Pravastatin 20 mg • Pravastatin 40 mg • Simvastatin 10 mg	20% to 30%
Medium intensity	• Atorvastatin 10 mg • Fluvastatin 80 mg • Rosuvastatin 5 mg • Simvastatin 20 mg • Simvastatin 40 mg	31% to 40%
High intensity	• Atorvastatin 20 mg • Atorvastatin 40 mg • Atorvastatin 80 mg • Rosuvastatin 10 mg • Rosuvastatin 20 mg • Rosuvastatin 40 mg • Simvastatin 80 mg	Greater than 40%

Source: Law 2003[141]

Thirty four studies were included in the review comparing UK licensed statins versus placebo (Table 39).[5,7-9,16,20,24,25,27,28,43,53,58,132,133,142,143,166,168,170,172,209,222,223,228,234,236,237,239,246,259,260,284,285] Evidence from these are summarised in the clinical GRADE evidence profiles below. Clinical evidence is presented firstly for statins versus placebo according to intensity (Table 41) and population (Table 43). Eighteen of these studies were conducted in secondary prevention populations[5,7,8,16,25,43,133,143,166,209,223,228,236,239,246,259,284,285], 11 studies in primary prevention populations[9,20,24,58,168,170,172,222,234,237,260], 3 studies in people with type 2 diabetics[28,53,132] and 2 studies in people with chronic kidney disease.[27,142] No studies were identified in people with type 1 diabetes.

Seventeen studies were included in the head-to-head statin comparison review (Table 40).[23,44,62,69,80,106,117,118,125,140,194,196-198,206,214,229,232,292] Fourteen studies were conducted in secondary prevention populations[23,44,62,69,80,106,118,125,140,194,196-198,206,229,292] and 3 studies in primary prevention populations.[117,214,232] The order for head-to-head comparisons is as follows: high versus low intensity (Table 45), high versus medium intensity (Table 46), medium versus low intensity (Table 47), high or medium versus low intensity (Table 48), low versus low intensity (Table 49) and high versus high

intensity (Table 50). No studies were identified in people with type 1 diabetes, type 2 diabetes and chronic kidney disease. Evidence from these are summarised in the clinical GRADE evidence profiles (Table 45, Table 46, Table 47, Table 48, Table 49 and Table 50).

Of the 34 studies identified that compared statin versus placebo (Table 39) only 16 reported final LDL-cholesterol values for both the statin and placebo arms (Table 51). [9,16,24,25,28,43,53,133,142,234,239,246,259,260,284,285] Of the 17 studies identified that compared higher dose statin versus lower dose statin (Table 40), only 11 reported final LDL-cholesterol values for both statin arms (Table 52).[80,106,117,118,194,196-198,206,214,229,232,292] Other studies reported LDL-cholesterol changes in alternative representations for example; percentage change from baseline levels, p value of change, final value in statin arm only, graphical representation only. Evidence for statin LDL-cholesterol reduction is summarised in Table 53, Table 54, Table 55, Table 56, Table 57, and Table 58.

No studies were identified that reported separate information on black and minority ethnic groups, people with a family history of CVD, autoimmune disease, serious mental illness or people in low socioeconomic groups.

See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 39: Summary of studies included in the statins versus placebo review

Study name	Stratum	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Amarenco 2006[16] SPARCL	Adults with established CVD	High-intensity statin	Atorvastatin 80 mg	2365	Placebo	2366	Median 4.9 years
Anderssen 2005[20] HYRIM	Adults without established CVD	Low-intensity statin	Fluvastatin 40 mg	283	Placebo	285	4 years
Anon 1994[5] 4S	Adults with established CVD	Medium-intensity statin	Simvastatin 20 mg	2221	Placebo	2223	5.4 years
Anon 1998[7] LIPID	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	4512	Placebo	4502	6.1 years
Anon 2000[8] GISSI	Adults with established CVD	Low-intensity statin	Pravastatin 20 mg	2138	No treatment	2133	Mean 23 months
Anon 2002[9] ALLHAT-LLT	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	5170	Placebo	5185	Mean 4.8 years
Asselbergs 2004[24] PREVEND-IT	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	433	Placebo	431	Mean 46 months
Athyros 2002[25] GREACE	Adults with established CVD	High-intensity statin	Atorvastatin 20 mg	800	Usual care	800	Mean 3 years
Baigent 2005[27] UK-HARP-I	Adults with CKD	Medium-intensity statin	Simvastatin 20 mg	224	Placebo	224	1 year
Beishuizen 2005[28]	Adults with type 2 diabetes	Medium-intensity statin	Simvastatin 20 mg	125	Placebo	125	2 years
Byington 1995[43] PLAC II	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	75	Placebo	76	3 years
Colhoun 2004[53] CARDS	Adults with type 2 diabetes	Medium-intensity statin	Atorvastatin 10 mg	1429	Placebo	1412	Median 3.9 years

Study name	Stratum	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
Crouse 2007[58] METEOR	Adults without established CVD	High-intensity statin	Rosuvastatin 40 mg	702	Placebo	282	2 years
Knopp 2006 [132] ASPEN	Adults with type 2 diabetes	Medium-intensity statin	Atorvastatin 10 mg	1211	Placebo	1199	Median 4 years
Koren 2004[133] ALLIANCE	Adults with established CVD	High-intensity statin	Atorvastatin 80 mg*	1217	Usual care	1225	Mean 51.5 months
Lemos 2003[143] LIPS	Adults with established CVD	Medium-intensity statin	Fluvastatin 80 mg	844	Placebo	833	3–4 years
Lemos 2013[142]	Adults with CKD	High-intensity statin	Rosuvastatin 10 mg	22	Placebo	29	2 years
Meade 1999[166] HPS	Adults with established CVD	Medium-intensity statin	Simvastatin 40 mg	10269	Placebo	10267	5 years
Mercuri 1996[168] CAIUS	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	151	Placebo	154	3 years
Mok 2009[170]	Adults without established CVD	Medium-intensity statin	Simvastatin 20 mg	113	Placebo	114	2 years
Nakamura 2006[172] MEGA	Adults without established CVD	Low-intensity statin	Pravastatin 20 mg	3866	Placebo	3966	Mean 5.3 years
Pitt 1995[209] PLAC I	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	206	Placebo	202	3 years
Ridker 2008[222] JUPITER	Adults without established CVD	High-intensity statin	Rosuvastatin 20 mg	8901	Placebo	8901	Median 1.9 years
Riegger 1999[223]	Adults with established CVD	Low-intensity statin	Fluvastatin 40 mg	187	Placebo	178	1 year
Sacks 1996[228] CARE	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	2081	Placebo	2078	5 years
Sever 2003[234]	Adults without	Medium-intensity statin	Atorvastatin 10 mg	5168	Placebo	5137	Median 3.3 years

Study name	Stratum	Intervention 1: class	Intervention 1: details	Number randomised intervention group	Comparison	Number randomised comparison group	Follow up
ASCOT-LLA	established CVD						
Shepherd 1995[237] WOSCOPS	Adults without established CVD	Low-intensity statin	Pravastatin 40 mg	3302	Placebo	3293	4.9 years
Shepherd 2002[236] PROSPER	Adults with established CVD	Low-intensity statin	Pravastatin 40 mg	2891	Placebo	2913	Mean 3.2 years
Shukla 2005[239]	Adults with established CVD	Medium-intensity statin	Atorvastatin 10 mg	75	Placebo	75	1 year
Sola 2006[246]	Adults with established CVD	High-intensity statin	Atorvastatin 20 mg	54	Placebo	54	1 year
Teo 2000[259] SCAT	Adults with established CVD	Low-intensity statin	Simvastatin 10 mg	230	Placebo	230	3-5 years
Terry 2007[260] CATZ	Adults without established CVD	High intensity	Simvastatin 80	40	Placebo	40	1 year
Yamada 2007[284]	Adults with established CVD	Medium-intensity statin	Atorvastatin 10 mg	19	Usual care	19	3 years
Yokoi 2005[285]	Adults with established CVD	Low-intensity statin	Pravastatin 20 mg	186	Usual care	187	3 years
* Koren 2004[133] ALLIANCE was a treat to target RCT. Participants were given atorvastatin up to 80 mg according to level of achieved LDL cholesterol The median daily dose used in the study was 40.5 mg and 45% of patients received the 80 mg dose). Note atorvastatin 40 mg and atorvastatin 80 mg are both classified as high-intensity statin.							

Table 40: Summary of studies included in the head-to-head review

Study name	Number patients	Population details	Intervention 1: class	Intervention 1: details	Intervention 2: class	Intervention 2: details	Follow up
Armitage 2010[23]	12,064	Post-MI	Medium-intensity	Simvastatin 20 mg/day	High-intensity	Simvastatin 80 mg/day	6.7 years

Study name	Number patients	Population details	Intervention 1: class	Intervention 1: details	Intervention 2: class	Intervention 2: details	Follow up
SEARCH			statin		statin		
Cannon 2004[44] PROVE IT TIMI 22	4162	Patients with ACS (18% diabetes)	Low-intensity statin	Pravastatin 40 mg/day	High-intensity statin	Atorvastatin 80 mg/day	2 years
de Lemos 2004[62] Phase Z of A to Z trial	4497	Patients with ACS (24% diabetes)	Medium-intensity statin	Placebo for 4 months followed by simvastatin 20 mg/day.	High-intensity statin	Simvastatin 40 mg/day for 1 month followed by simvastatin 80 mg/day.	2 years
Deedwania 2007[69]	891	Patients with history of CAD (23% diabetes)	Low-intensity statin	Pravastatin 40 mg/day	High-intensity statin	Atorvastatin 80 mg/day	1 year
Egede 2013[80] VIRHISTAMI	87	Patients with STEMI	High-intensity statin	Rosuvastatin 40 mg/day	High-intensity statin	Rosuvastatin 5 mg/day	1 year
Gottlieb 2008[106]	31	Patients with established moderate-to-severe atherosclerosis	Medium-intensity statin	Simvastatin 20 mg/day	High-intensity statin	Simvastatin 80 mg/day	1 year
Hong 2008[118]	30	Patients with angina	High-intensity statin	Atorvastatin 40 mg/day	High-intensity statin	Rosuvastatin 20 mg/day	1 year
Hong 2009[117]	100	Patients without established CVD	Medium-intensity statin	Simvastatin 20 mg/day	High-intensity statin	Rosuvastatin 10 mg/day	1 year
Ito 2001[125] PATE	665	Overall (30% diabetes)	Low-intensity statin	Pravastatin 5 mg/day	Low-intensity statin	Pravastatin 10–20 mg/day	3.9 years
Larosa 2005[140] TNT	10,001	Patients with stable CHD (15% diabetes)	Medium-intensity statin	Atorvastatin 10 mg/day	High-intensity statin	Atorvastatin 80 mg/day	4.9 years
Nicholls 2011[194] SATURN	1385	Patients with coronary disease (15% diabetes)	High-intensity statin	Atorvastatin 80 mg/day	High-intensity statin	Rosuvastatin 40 mg/day	2 years
Nissen 2005[196-198] REVERSAL	654	Patients requiring coronary angiography	Low-intensity statin	Pravastatin 40 mg/day	High-intensity statin	Atorvastatin 80 mg/day	18 months
Pedersen 2005[206]	8888	Post-MI (12%	Medium-intensity	Simvastatin 20 mg/day.	High-intensity	Atorvastatin 80 mg/day.	4.8 years

Study name	Number patients	Population details	Intervention 1: class	Intervention 1: details	Intervention 2: class	Intervention 2: details	Follow up
IDEAL		diabetes)	statin	If, at 24 weeks, total-C >190 mg/dl (5.0 mmol/litre), 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.	statin	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.	
Raggi 2005[214]	615	Hyperlipidaemic post-menopausal women	Low-intensity statin	Pravastatin 40 mg/day	High-intensity statin	Atorvastatin 80 mg/day	1 year
Satoh 2009[229]	100	Patients with CAD	Low-intensity statin	Pravastatin 10 mg/day	Medium-intensity statin	Atorvastatin 10 mg/day	1 year
Schmermund 2006[232]	471	Patients with ≥ 2 CV factors and moderate calcified coronary atherosclerosis	Medium-intensity statin	Atorvastatin 10 mg/day	High-intensity statin	Atorvastatin 80 mg/day	1 year
Zou 2003[292]	197	Patients with ACS (14% diabetes)	Low-intensity statin	Simvastatin 10 mg/day	Medium-intensity statin	Simvastatin 20 mg/day	1 year

11.3.1 Clinical evidence profiles for the outcomes of mortality, CV events and adverse events

Clinical evidence is presented firstly for statins versus placebo according to intensity (Table 41, Table 42) and population (Table 43, Table 44). The order for head to head comparisons is as follows; high intensity versus low intensity (Table 45), high intensity versus medium intensity (Table 46), medium versus low intensity (Table 47), high or medium versus low intensity (Table 48), low versus low intensity (Table 49) and high versus high intensity (Table 50).

Table 41: Clinical evidence profile: statins versus placebo (subgroup analysis by statin intensity)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	Placebo (by intensity)	Relative (95% CI)	Absolute		
All-cause mortality - Combined intensity studies[5,7,8,10,16,20,25,28,43,53,58,132,133,143,166,170,172,209,222,228,234,236,237,246,259,285]												
26	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4292/60352 (7.1%)	4916/59977 (8.2%)	RR 0.87 (0.84 to 0.91)	11 fewer per 1000 (from 7 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Low intensity versus placebo[7,8,10,20,43,172,209,228,236,237,259,285]												
12	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1865/24936 (7.5%)	2102/25042 (8.4%)	RR 0.89 (0.84 to 0.94)	9 fewer per 1000 (from 5 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Medium intensity versus placebo[5,28,53,132,143,166,170,234]												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1864/21379 (8.7%)	2185/21308 (10.3%)	RR 0.85 (0.80 to 0.9)	15 fewer per 1000 (from 10 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - High intensity versus placebo[16,25,58,133,222,246]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	563/14037 (4%)	629/13627 (4.6%)	RR 0.9 (0.8 to 1)	5 fewer per 1000 (from 9 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality- Combined intensity studies versus placebo[5,7,8,10,16,24,25,53,132,133,143,166,172,209,221,223,228,234,236,237,259,284]												
22	randomised	no serious	no serious	no serious	no serious	none	2347/59459	2882/59459	RR 0.81	9 fewer per 1000	⊕⊕⊕⊕	CRITICAL

	trials	risk of bias	inconsistency	indirectness	imprecision		(3.9%)	(4.8%)	(0.77 to 0.86)	(from 7 fewer to 11 fewer)	HIGH	
CV mortality - Low intensity versus placebo[7,8,10,24,172,209,223,228,236,237,259]												
11	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1101/25016 (4.4%)	1315/25111 (5.2%)	RR 0.84 (0.78 to 0.91)	8 fewer per 1000 (from 5 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - Medium intensity versus placebo[5,53,132,143,166,234,284]												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1060/21160 (5.0%)	1313/21088 (6.2%)	RR 0.81 (0.75 to 0.87)	12 fewer per 1000 (from 8 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - High intensity versus placebo[16,25,133,221]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	186/13283 (1.4%)	254/13292 (1.9%)	RR 0.73 (0.61 to 0.88)	5 fewer per 1000 (from 2 fewer to 7 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI - Combined intensity studies[5,7,8,24,25,28,43,53,58,133,166,168,172,209,222,223,228,236,237,259,285]												
21	randomised trials	no serious risk of bias	Serious[b]	no serious indirectness	no serious imprecision	none	1593/45915 (3.5%)	2318/45567 (5.1%)	RR 0.69 (0.65 to 0.73)	16 fewer per 1000 (from 14 fewer to 18 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI - Low intensity versus placebo[7,8,24,43,168,172,209,223,228,236,237,259,285]												
13	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	951/20254 (4.7%)	1222/20335 (6%)	RR 0.78 (0.72 to 0.84)	13 fewer per 1000 (from 10 fewer to 17 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI - Medium intensity versus placebo[5,28,53,166]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	552/14043 (3.2%)	898/14025 (6.3%)	RR 0.61 (0.55 to 0.68)	25 fewer per 1000 (from 20 fewer to 29 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - High intensity versus placebo[25,58,133,222]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	96/11618 (0.83%)	207/11207 (1.8%)	RR 0.46 (0.37 to 0.59)	10 fewer per 1000 (from 8 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Stroke - Combined intensity studies versus placebo[5,7,8,10,16,24,25,53,133,166,170,172,209,222,228,234,236,237,259,285]												
19	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	1456/54602 (2.7%)	1867/54642 (3.4%)	RR 0.78 (0.73 to 0.83)	8 fewer per 1000 (from 6 fewer to 9 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Low intensity versus placebo[7,8,10,24,172,209,228,237,259,285]												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	499/22120 (2.3%)	597/22199 (2.7%)	RR 0.84 (0.75 to 0.94)	4 fewer per 1000 (from 2 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke - Medium intensity versus placebo[5,53,166,170,234]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	618/19199 (3.2%)	844/19151 (4.4%)	RR 0.73 (0.66 to 0.81)	12 fewer per 1000 (from 8 fewer to 15 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - High intensity versus placebo[16,25,133,222]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	339/13283 (2.6%)	425/13292 (3.2%)	RR 0.8 (0.7 to 0.91)	6 fewer per 1000 (from 3 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Myalgia - Combined intensity studies versus placebo[8,16,25,28,53,58,132,236,237]												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	348/14960 (2.3%)	288/14520 (2%)	RR 1.02 (0.88 to 1.19)	0 more per 1000 (from 2 fewer to 4 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Myalgia - Low intensity versus placebo[8,236,237]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[c]	none	62/8331 (0.74%)	51/8339 (0.61%)	RR 1.22 (0.84 to 1.76)	1 more per 1000 (from 1 fewer to 5 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Myalgia - Medium intensity versus placebo[28,53,132]												
3	randomised trials	no serious risk of bias	Serious[d]	no serious indirectness	Serious[c]	none	68/2764 (2.5%)	62/2734 (2.3%)	RR 1.09 (0.78 to 1.52)	2 more per 1000 (from 5 fewer to 12 more)	⊕⊕OO LOW	LESS IMPORTANT
Myalgia - High intensity versus placebo[16,25,58]												

3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	218/3865 (5.6%)	175/3447 (5.1%)	RR 0.95 (0.78 to 1.16)	3 fewer per 1000 (from 11 fewer to 8 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Liver adverse events - Combined intensity studies versus placebo [5,8,9,16,25,27,28,53,58,132,143,166,170,222,236,237]												
16	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	282/42702 (0.66%)	146/42267 (0.35%)	RR 1.9 (1.56 to 2.32)	3 more per 1000 (from 2 more to 5 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Liver adverse events - Low intensity versus placebo [8,9,25,132,236,237]												
6	randomised trials	no serious risk of bias	Serious[e]	no serious indirectness	no serious imprecision	none	93/16140 (0.58%)	45/16133 (0.28%)	RR 2.03 (1.43 to 2.88)	3 more per 1000 (from 1 more to 5 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events - Medium intensity versus placebo [5,27,28,143,166,170]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[c]	none	104/13796 (0.75%)	69/13786 (0.5%)	RR 1.5 (1.11 to 2.03)	3 more per 1000 (from 1 more to 5 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events - High intensity versus placebo [16,25,58,222]												
4	randomised trials	no serious risk of bias	Serious[f]	no serious indirectness	no serious imprecision	none	85/12766 (0.67%)	32/12348 (0.26%)	RR 2.57 (1.71 to 3.85)	4 more per 1000 (from 2 more to 7 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
New onset diabetes - Combined intensity studies versus placebo [5,7-9,166,172,222,234,236,237]												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1829/38996 (4.7%)	1675/39021 (4.3%)	RR 1.09 (1.03 to 1.17)	4 more per 1000 (from 1 more to 7 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
New onset diabetes - Low intensity versus placebo [7-9,172,236,237]												
6	randomised trials	no serious risk of bias	Serious[g]	no serious indirectness	no serious imprecision	none	872/16778 (5.2%)	839/16849 (5%)	RR 1.05 (0.95 to 1.15)	2 more per 1000 (from 2 fewer to 7 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
New onset diabetes - Medium intensity versus placebo [5,166,234]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	687/13317 (5.2%)	620/13271 (4.7%)	RR 1.11 (1 to 1.23)	5 more per 1000 (from 0 more to 11	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

										more)		
New onset diabetes - High intensity versus placebo[221]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[c]	none	270/8901 (3%)	216/8901 (2.4%)	RR 1.25 (1.05 to 1.49)	6 more per 1000 (from 1 more to 12 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Rhabdomyolysis - Combined intensity studies versus placebo [5,16,20,27,28,53,58,132,133,143,166,170,222,223,234,236]												
16	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[h]	none	24/38147 (0.06%)	18/37754 (0.05%)	RR 1.21 (0.69 to 2.12)	0 more per 1000 (from 0 fewer to 1 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis - Low intensity versus placebo[20,223,236]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[h]	none	0/3361 (0%)	2/3376 (0.06%)	RR 0.33 (0.03 to 3.13)	0 fewer per 1000 (from 1 fewer to 1 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis - Medium intensity versus placebo[5,27,28,53,132,166,170,236]												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[c]	none	20/21603 (0.09%)	11/21532 (0.05%)	RR 1.72 (0.85 to 3.44)	0 more per 1000 (from 0 fewer to 1 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Rhabdomyolysis - High intensity versus placebo[16,58,133,222]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[h]	none	4/13183 (0.03%)	5/12773 (0.04%)	RR 0.64 (0.2 to 2.09)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	LESS IMPORTANT

[a]*Confidence interval of the estimate of effect crosses 1 default MID (0.75).*
[b]*I^2= 63%.*
[c]*Confidence interval of the estimate of effect crosses 1 default MID (1.25).*
[d]*I^2= 72%.*
[e]*I^2=65%.*
[f]*I^2 = 60%.*
[g]*I^2 = 51%.*
[h]*Confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*

Table 42: Time-to-event results for statins versus placebo (subgroup analysis by statin intensity)

Study	Statin and dose	Intensity of statin	Outcome, HR (95%C)	Number of studies
Anon 1998[7]LIPID	Pravastatin 40 mg	Low	All-cause mortality; 0.85 (0.78 to 0.92)	5
Nakamura 2006[172] MEGA	Pravastatin 20 mg			
Sacks 1996[228] CARE	Pravastatin 40 mg			
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Anon 1994[5] 4S	Simvastatin 20 mg	Medium	All-cause mortality; 0.77 (0.68 to 0.87)	3
Colhoun 2004[53] CARDS	Atorvastatin 10 mg			
Sever 2003[234] ASCOT-LLA	Atorvastatin 10 mg			
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	High	All-cause mortality; 0.67 (0.48 to 0.93)	3
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Low	CV mortality; 0.67 (0.48 to 0.93)	2
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Sever 2003[234] ASCOT-LLA	Atorvastatin 10 mg	Medium	CV mortality; 0.90 (0.66 to 1.23)	1
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	High	CV mortality; 0.75 (0.59 to 0.94)	2
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Low	Non-fatal MI; 0.77 (0.68 to 0.87)	4
Sacks 1996[228] CARE	Pravastatin 40 mg			
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg	High	Non-fatal MI; 0.45 (0.35 to 0.58)	2
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Low	Stroke; 0.87 (0.72 to 1.05)	4
Sacks 1996[228] CARE	Pravastatin 40 mg			
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Anon 1994[5] 4S	Simvastatin 20 mg	Medium	Stroke; 0.68 (0.54 to 0.86)	2
Sever 2003[234] ASCOT-LLA	Atorvastatin 10 mg			
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	High	Stroke; 0.80 (0.69 to 0.92)	3

Study	Statin and dose	Intensity of statin	Outcome, HR (95%C)	Number of studies
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			

Table 43: Clinical evidence profile: statins versus placebo (subgroup analysis by strata)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	Placebo (by strata)	Relative (95% CI)	Absolute		
All-cause mortality - Adults with established CVD[5,7,8,16,25,43,133,143,166,209,228,236,246,259,285]												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2978/30085 (9.9%)	3436/30081 (11.4%)	RR 0.87 (0.83 to 0.91)	15 fewer per 1000 (from 10 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Adults without established CVD[8,20,58,170,172,222,234,237]												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1180/27503 (4.3%)	1326/27162 (4.9%)	RR 0.89 (0.83 to 0.96)	5 fewer per 1000 (from 2 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Adults with type 2 diabetes[5,28,53,132]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	149/2869 (5.2%)	178/2831 (6.3%)	RR 0.82 (0.67 to 1.01)	11 fewer per 1000 (from 21 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality - Adults with CKD[222,228]												
2	randomised trials	no serious risk of bias	Serious[b]	no serious indirectness	serious[a]	none	120/2482 (4.8%)	172/2496 (6.9%)	RR 0.71 (0.57 to 0.89)	20 fewer per 1000 (from 8 fewer to 30 fewer)	⊕⊕OO LOW	CRITICAL
CV mortality - Adults with established CVD[5,7,8,16,25,133,143,166,209,223,228,236,259,284]												
14	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1812/29980 (6%)	2287/29969 (7.6%)	RR 0.79 (0.75 to 0.84)	16 fewer per 1000 (from 12 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - Adults without established CVD[10,172,222,234,237]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	430/17506 (1.8%)	473/17581 (2.0%)	RR 0.90 (0.79 to 1.01)	2 fewer per 1000 (from 4 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - Adults with type 2 diabetes[5,53,132,228]												

4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	95/3026 (3.1%)	111/3010 (3.7%)	RR 0.86 (0.66 to 1.12)	5 fewer per 1000 (from 13 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality - Adults with CKD[24]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	4/443 (0.92%)	4/431 (0.93%)	RR 1.00 (0.25 to 3.95)	0 more per 1000 (from 7 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Non-fatal MI - Adults with established CVD[5,7,8,25,43,133,166,209,223,228,236,259,285]												
13	randomised trials	no serious risk of bias	Serious[d]	no serious indirectness	no serious imprecision	none	1377/27009 (5.1%)	1960/27006 (7.3%)	RR 0.7 (0.66 to 0.75)	22 fewer per 1000 (from 18 fewer to 25 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI - Adults without established CVD[58,168,172,222,237]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	183/16920 (1.1%)	298/16595 (1.8%)	RR 0.61 (0.51 to 0.73)	7 fewer per 1000 (from 5 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - Adults with type 2 diabetes[5,28,53]												
4	randomised trials	no serious risk of bias	Serious[e]	no serious indirectness	serious[a]	none	60/1940 (3.1%)	106/1936 (5.5%)	RR 0.57 (0.42 to 0.78)	24 fewer per 1000 (from 12 fewer to 32 fewer)	⊕⊕OO LOW	CRITICAL
Non-fatal MI - Adults with CKD[24,222,228]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	81/2915 (2.8%)	125/2927 (4.3%)	RR 0.66 (0.50 to 0.86)	15 fewer per 1000 (from 6 fewer to 21 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Adults with established CVD[7,8,10,24,172,209,228,237,259,285]												
11	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	1060/26221 (4%)	1356/26205 (5.2%)	RR 0.78 (0.72 to 0.84)	11 fewer per 1000 (from 8 fewer to 14 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Adults without established CVD[8,170,172,222,234,237]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	368/26520 (1.4%)	467/26596 (1.8%)	RR 0.79 (0.69 to 0.9)	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Adults with type 2 diabetes [7,53,166,228]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	223/5230 (4.3%)	309/5234 (5.9%)	RR 0.72 (0.61 to 0.86)	17 fewer per 1000 (from 8 fewer to 23 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Stroke - Adults with CKD[24,222,228]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	46/2915 (1.6%)	65/2927 (2.2%)	RR 0.73 (0.5 to 1.06)	6 fewer per 1000 (from 11 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
Myalgia - Adults with established CVD[8,16,25,236]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	171/8194 (2.1%)	173/8212 (2.1%)	RR 0.99 (0.81 to 1.22)	0 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Myalgia - Adults without established CVD[58,237]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[f]	none	109/4002 (2.7%)	53/3574 (1.5%)	RR 1.05 (0.76 to 1.45)	1 more per 1000 (from 4 fewer to 7 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Myalgia - Adults with type 2 diabetes[28,53,228]												
3	randomised trials	no serious risk of bias	Serious[g]	no serious indirectness	serious[f]	none	68/2764 (2.5%)	62/2734 (2.3%)	RR 1.09 (0.78 to 1.52)	2 more per 1000 (from 5 fewer to 12 more)	⊕⊕OO LOW	LESS IMPORTANT
Myalgia - Adults with CKD[222]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	292/1638 (17.8%)	303/1629 (18.6%)	RR 0.96 (0.83 to 1.11)	7 fewer per 1000 (from 32 fewer to 20 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Liver adverse events - Adults with established CVD[5,8,16,25,143,166,236]												
7	randomised trials	no serious risk of bias	Serious[h]	no serious indirectness	no serious imprecision	none	175/21528 (0.81%)	84s/21535 (0.4%)	RR 2.10 (1.62 to 2.72)	4 more per 1000 (from 2 more to 7 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events - Adults without established CVD[20,58,170,222,234]												
5	randomised trials	no serious risk of bias	Serious[d]	no serious indirectness	no serious imprecision	none	64/18186 (0.35%)	30/17774 (0.17%)	RR 2.03 (1.32 to 3.12)	2 more per 1000 (from 1 more to 4 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events - Adults with type 2 diabetes[5,28,53,166]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[f]	none	55/5742 (0.96%)	43/5719 (0.75%)	RR 1.27 (0.85 to 1.88)	2 more per 1000 (from 1 fewer to 7 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events - Adults with CKD[27,222,228]												

3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	9/2706 (0.3%)	10/2720 (0.4%)	RR 0.91 (0.37 to 2.24)	0 fewer per 1000 (from 2 fewer to 5 more)	⊕⊕OO LOW	LESS IMPORTANT
New onset diabetes - Adults with established CVD[5,7,8,166,236]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	920/17156 (5.4%)	856/17139 (5%)	RR 1.07 (0.98 to 1.18)	3 more per 1000 (from 1 fewer to 9 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
New onset diabetes - Adults without established CVD[10,172,222,234,237]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	909/21840 (4.2%)	819/21882 (3.7%)	RR 1.12 (1.02 to 1.22)	4 more per 1000 (from 1 more to 8 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
New onset diabetes - Adults with type 2 diabetes												
0	Not applicable						-	-				LESS IMPORTANT
New onset diabetes - Adults with CKD												
0	No evidence available						-	-				LESS IMPORTANT
Rhabdomyolysis - Adults with established CVD[5,16,133,143,166,223,236]												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	19/19994 (0.1%)	14/20005 (0.07%)	RR 1.33 (0.68 to 2.59)	0 more per 1000 (from 0 fewer to 1 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis - Adults without established CVD[20,58,170,222,234]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	3/15165 (0.02%)	3/14718 (0.02%)	RR 0.76 (0.22 to 2.58)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis - Adults with type 2 diabetes[28,53,132,166]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	5/5742 (0.09%)	3/5719 (0.05%)	RR 1.67 (0.4 to 6.96)	0 more per 1000 (from 0 fewer to 3 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis - Adults with CKD[27,222,228]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[f]	none	10/2706 (0.37%)	3/2720 (0.11%)	RR 2.79 (0.89 to 8.78)	2 more per 1000 (from 0 fewer to 9 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT

[a]Confidence interval of the estimate of effect crosses 1 default MID (0.75).

[b]*I^2= 52%.*
[c]*Confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*
[d]*I^2= 60%.*
[e]*I^2=57%.*
[f]*Confidence interval of the estimate of effect crosses 1 default MID (1.25).*
[g]*I^2= 72%.*
[h]*I^2= 52%.*

Table 44: Time to event results for statins versus placebo (subgroup analysis by statin intensity)

Study	Statin and dose	Intensity	Outcome, HR (95%C)	Number of studies
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	With CVD	All-cause mortality; 0.86 (0.80 to 0.93) 0.86 [0.80, 0.93]	5
Anon 1994[5] 4S	Simvastatin 20 mg			
Anon 1998[7]LIPID	Pravastatin 40 mg			
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Without CVD	All-cause mortality; 0.81 (0.72 to 0.90)	4
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			
Sever 2003[234] ASCOT-LLA	Pravastatin 40 mg			
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Colhoun 2004[53] CARDS	Atorvastatin 10 mg	Type 1 diabetes	All-cause mortality; 0.73 (0.52 to 1.02)	1
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg	CKD	All-cause mortality; 0.72 (0.57 to 0.94)	2
Sacks 1996[228] CARE	Pravastatin 40 mg			
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	With CVD	CV mortality; 0.75 (0.59 to 0.94)	2
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Without CVD	CV mortality; 0.78 (0.63 to 0.98)	3
Sever 2003[234] ASCOT-LLA	Pravastatin 40 mg			
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg	With CVD	Non-fatal MI; 0.76 (0.65 to 0.89)	2
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Without CVD	Non-fatal MI; 0.60 (0.50 to 0.73)	3
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			
Shepherd 1995[237] WOSCOPS	Pravastatin 40 mg			
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg	CKD	Non-fatal MI; 0.67 (0.49 to 0.92)	2
Sacks 1996[228] CARE	Pravastatin 40 mg			
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	With CVD	Stroke; 0.88 (0.77 to 1.01)	3
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Shepherd 2002[236] PROSPER	Pravastatin 40 mg			
Nakamura 2006[172] MEGA	Pravastatin 20 mg	Without CVD	Stroke; 0.77 (0.58 to 0.86)	3
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg			

Study	Statin and dose	Intensity	Outcome, HR (95%C)	Number of studies
Sever 2003[234] ASCOT-LLA	Pravastatin 40 mg			
Colhoun 2004[53] CARDS	Atorvastatin 10 mg	Type 2 diabetes	Stroke; 0.52 (0.31 to 0.87)	1
Ridker 2008[222] JUPITER	Rosuvastatin 20 mg	CKD	Stroke; 0.64 (0.43 to 0.96)	2
Sacks 1996[228] CARE	Pravastatin 40 mg			

Table 45: Clinical evidence profile: high intensity (atorvastatin 80 mg) versus low intensity (pravastatin 40 mg) for the secondary prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-intensity statin	High-intensity statin	Relative (95% CI)	Absolute		
All-cause mortality;[44,69]												
2	randomised trials	no serious risk of bias	serious[a]	no serious indirectness	serious[b]	none	52/2545 (2%)	84/2508 (3.3%)	RR 0.61 (0.43 to 0.86)	13 fewer per 1000 (from 5 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
CV mortality[44,69]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	27/2544 (1.1%)	39/2508 (1.6%)	RR 0.68 (0.42 to 1.11)	5 fewer per 1000 (from 9 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI[44]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	139/2099 (6.6%)	153/2063 (7.4%)	RR 0.89 (0.72 to 1.11)	8 fewer per 1000 (from 21 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke[44,69]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	22/2545 (0.86%)	24/2508 (0.96%)	RR 0.9 (0.51 to 1.6)	1 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Myalgia[69]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	8/446 (1.8%)	5/445 (1.1%)	RR 1.6 (0.53 to 4.84)	7 more per 1000 (from 5 fewer to 43 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis[44,69,214]												

3	randomised trials	no serious risk of bias	very serious[d]	no serious indirectness	serious[e]	none	7/2763 (0.25%)	1/2765 (0.04%)	RR 4.39 (0.98 to 19.72)	1 more per 1000 (from 0 fewer to 7 more)	⊕OOO VERY LOW	LESS IMPORTANT
Liver[44,69,214]												
3	randomised trials	no serious risk of bias	serious[f]	no serious indirectness	no serious imprecision	none	89/2545 (3.5%)	24/2508 (0.96%)	RR 3.61 (2.31 to 5.65)	25 more per 1000 (from 13 more to 44 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT

[a] *I^2= 52%.*

[b] *Confidence interval of the estimate of effect crosses 1 default MID (0.75).*

[c] *Confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*

[d] *I^2= 71%*

[e] *Confidence interval of the estimate of effect crosses 1 default MID (1.25).*

[f] *I^2= 70%.*

Table 46: Clinical evidence profile: high intensity (atorvastatin 80 mg or simvastatin 80 mg) versus medium intensity (atorvastatin 10 mg or simvastatin 20 mg) statin for the secondary prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-intensity statin	Medium-intensity statin	Relative (95% CI)	Absolute		
All-cause mortality- all studies [23,62,140,206]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1678/17562 (9.6%)	1711/17543 (9.8%)	RR 0.98 (0.92 to 1.04)	2 fewer per 1000 (from 8 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - atorvastatin 80 mg versus atorvastatin 10 mg[140]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	132/3225 (4.1%)	124/3324 (3.7%)	RR 1.1 (0.86 to 1.4)	4 more per 1000 (from 5 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality – people with CKD - atorvastatin 80 mg versus atorvastatin 10 mg[140]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/1602 (7%)	113/1505 (7.5%)	RR 0.93 (0.72 to 1.2)	5 fewer per 1000 (from 21 fewer to 15 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality – atorvastatin 10 mg versus simvastatin 80 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	366/4439 (8.2%)	374/4449 (8.4%)	RR 0.98 (0.85 to 1.13)	2 fewer per 1000 (from 13 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - simvastatin 80 mg versus simvastatin 20 mg[23,62]												
2	randomised trials	no serious risk of bias	serious[b]	no serious indirectness	no serious imprecision	none	1068/8296 (12.9%)	1100/8265 (13.3%)	RR 0.97 (0.9 to 1.05)	4 fewer per 1000 (from 13 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality- all studies[23,62,140,206]												

4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	972/17730 (5.5%)	1026/17720 (5.8%)	RR 0.95 (0.87 to 1.03)	3 fewer per 1000 (from 8 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - atorvastatin 80 versus atorvastatin 10 mg[140]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	none	101/4995 (2%)	127/5006 (2.5%)	RR 0.8 (0.62 to 1.03)	5 fewer per 1000 (from 10 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality - atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/4439 (5%)	218/4449 (4.9%)	RR 1.03 (0.85 to 1.23)	1 more per 1000 (from 7 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality - simvastatin 80 mg versus simvastatin 20 mg[23,62]												
2	randomised trials	no serious risk of bias	serious[d]	no serious indirectness	no serious imprecision	none	648/8296 (7.8%)	681/8265 (8.2%)	RR 0.95 (0.86 to 1.05)	4 fewer per 1000 (from 12 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI- all studies[23,62,140,206]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1058/17730 (6%)	1247/17720 (7%)	RR 0.85 (0.78 to 0.92)	11 fewer per 1000 (from 6 fewer to 15 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - atorvastatin 80 mg versus atorvastatin 10 mg[140]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	243/4995 (4.9%)	308/5006 (6.2%)	RR 0.79 (0.67 to 0.93)	13 fewer per 1000 (from 4 fewer to 20 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	267/4439 (6%)	321/4449 (7.2%)	RR 0.83 (0.71 to 0.98)	12 fewer per 1000 (from 1 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - simvastatin 80 mg versus simvastatin 20 mg[23,62]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	548/8296 (6.6%)	618/8265 (7.5%)	RR 0.88 (0.79 to	9 fewer per 1000 (from 1 fewer to	⊕⊕⊕⊕ HIGH	CRITICAL

									0.99)	16 fewer)		
Stroke – all studies[23,62,206]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	388/12735 (3%)	439/12714 (3.5%)	RR 0.88 (0.77 to 1.01)	4 fewer per 1000 (from 8 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke – atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	151/4439 (3.4%)	174/4449 (3.9%)	RR 0.87 (0.7 to 1.08)	5 fewer per 1000 (from 12 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke – simvastatin 80 mg versus simvastatin 20 mg[23,62]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	237/8296 (2.9%)	265/8265 (3.2%)	RR 0.89 (0.75 to 1.06)	4 fewer per 1000 (from 8 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Myalgia – all studies[206,232]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	104/4673 (2.2%)	56/4682 (1.2%)	RR 1.86 (1.35 to 2.57)	10 more per 1000 (from 4 more to 19 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Myalgia – atorvastatin 80 mg versus atorvastatin 10 mg[232]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[e]	none	7/234 (3%)	5/233 (2.1%)	RR 1.39 (0.45 to 4.33)	8 more per 1000 (from 12 fewer to 71 more)	⊕⊕OO LOW	LESS IMPORTANT
Myalgia –atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/4439 (2.2%)	51/4449 (1.1%)	RR 1.91 (1.36 to 2.67)	10 more per 1000 (from 4 more to 19 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Rhabdomyolysis – all studies[23,62,206,232]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/17794 (0.3%)	13/17774 (0.07%)	RR 4.15 (2.27 to 7.59)	2 more per 1000 (from 1 more to 5 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

Rhabdomyolysis – atorvastatin 80 mg versus atorvastatin 10 mg[62,232]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/3459 (0%)	0/3557 (0%)	LESS pooled	LESS pooled	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Rhabdomyolysis – people with CKD – atorvastatin 80 mg versus atorvastatin 10 mg[62]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/1602 (0%)	0/1505 (0%)	LESS pooled	LESS pooled	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Rhabdomyolysis - atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/4439 (0%)	0/4449 (0%)	LESS pooled	LESS pooled	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Rhabdomyolysis – simvastatin 80 mg versus simvastatin 20 mg[23,62]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/8294 (0.65%)	13/8263 (0.16%)	RR 4.15 (2.27 to 7.59)	5 more per 1000 (from 2 more to 10 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Liver adverse events – all studies[23,62,140,206]												
4	randomised trials	no serious risk of bias	serious[f]	no serious indirectness	no serious imprecision	none	124/11632 (1.1%)	24/11579 (0.21%)	RR 5.15 (3.32 to 7.96)	9 more per 1000 (from 5 more to 14 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events – atorvastatin 80 mg versus atorvastatin 10 mg[140,232]												
2	randomised trials	no serious risk of bias	serious[g]	no serious indirectness	no serious imprecision	none	40/3459 (1.2%)	10/3557 (0.28%)	RR 4.1 (2.06 to 8.19)	9 more per 1000 (from 3 more to 20 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events – people with CKD – atorvastatin 80 mg versus atorvastatin 20 mg[62]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[h]	none	22/1602 (1.4%)	1/1505 (0.07%)	RR 20.67 (2.79 to 153.14)	13 more per 1000 (from 1 more to 101 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Liver adverse events – atorvastatin 80 mg versus simvastatin 20 mg[206]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/4439 (0.97%)	5/4449 (0.11%)	RR 8.62 (3.42 to	9 more per 1000 (from 3 more to 23	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

									21.74)	more)		
Liver adverse events – simvastatin 80 mg versus simvastatin 20 mg[62]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	19/2132 (0.89%)	8/2068 (0.39%)	RR 2.3 (1.01 to 5.25)	5 more per 1000 (from 0 more to 16 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
New-onset diabetes – simvastatin 80 mg versus simvastatin 20 mg[23]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	633/6031 (10.5%)	591/6033 (9.8%)	RR 1.07 (0.96 to 1.19)	7 more per 1000 (from 4 fewer to 19 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

[a]*Confidence interval of the estimate of effect crosses 1 default MID (1.25).*
[b]*I^2= 69%.*
[c]*Confidence interval of the estimate of effect crosses 1 default MID (1.25).*
[d]*I^2= 66%.*
[e]*Confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*
[f]*I^2= 58%.*
[g]*I^2= 55%.*
[h]*Very wide confidence interval for the estimate of effect.*

Table 47: Clinical evidence profile: medium intensity (simvastatin 20 mg) versus low intensity (simvastatin 10 mg) statin for the secondary prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medium-intensity statin	Low-intensity statin	Relative (95% CI)	Absolute		
CV mortality[292]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/99 (2%)	2/98 (2%)	RR 0.99 (0.14 to 6.89)	0 fewer per 1000 (from 18 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI[292]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7/99 (7.1%)	12/98 (12.2%)	RR 0.58 (0.24 to 1.41)	51 fewer per 1000 (from 93 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL

[a]*Patients not blinded; high rate of missing data.*
[b]*The confidence interval of the estimate of the effect crosses 2 default MIDs (0.75 and 1.25).*

Table 48: Clinical evidence profile: high intensity (atorvastatin 80 mg) or medium intensity (simvastatin 20 mg) versus low intensity (simvastatin 10 mg or pravastatin 40 mg) statin for prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medium-/high-intensity statin	Low-intensity statin	Relative (95% CI)	Absolute		
CV mortality[44,69,292]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	29/2643 (1.1%)	41/2606 (1.6%)	RR 0.7 (0.43 to 1.12)	5 fewer per 1000 (from 9 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Non-fatal MI[44,292]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	146/2198 (6.6%)	165/2161 (7.6%)	RR 0.87 (0.7 to 1.08)	10 fewer per 1000 (from 23 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

[a] *1 study patients were not blinded and high rate of missing data.*
[b] *The confidence interval of the estimate of effect crosses 1 default MID (0.75).*

Table 49: Clinical evidence profile: low intensity (pravastatin 20 mg) versus low intensity (pravastatin 5 mg) statin for prevention of CVD (overall – primary and secondary prevention)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low intensity Pravastatin 20 mg	Low intensity Pravastatin 5 mg	Relative (95% CI)	Absolute		
All-cause mortality[125]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	20/334 (6%)	14/331 (4.2%)	RR 1.42 (0.73 to 2.76)	18 more per 1000 (from 11 fewer to 74 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality[125]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	6/334 (1.8%)	8/331 (2.4%)	RR 0.74 (0.26 to 2.12)	6 fewer per 1000 (from 18 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Non-fatal MI[125]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	4/334 (1.2%)	1/331 (0.3%)	RR 3.96 (0.45 to 35.28)	9 more per 1000 (from 2 fewer to 104 more)	⊕⊕OO LOW	CRITICAL

[a]*The confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*

Table 50: Clinical evidence profile: high intensity (atorvastatin 80 mg) versus high intensity (rosuvastatin 20 or 40 mg) statin for the secondary prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High intensity Atorvastatin	High intensity Rosuvastatin	Relative (95% CI)	Absolute		
CV mortality - atorvastatin 80 mg versus rosuvastatin 40 mg[194]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	2/689 (0.29%)	2/691 (0.29%)	RR 1 (0.14 to 7.1)	0 fewer per 1000 (from 2 fewer to 18 more)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI - atorvastatin 80 mg versus rosuvastatin 40 mg[194]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	11/689 (1.6%)	11/691 (1.6%)	RR 1 (0.44 to 2.3)	0 fewer per 1000 (from 9 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Liver adverse events - atorvastatin 80 mg versus rosuvastatin 40 mg[194]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	14/668 (2.1%)	5/668 (0.75%)	RR 2.8 (1.01 to 7.73)	13 more per 1000 (from 0 more to 50 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Rhabdomyolysis – atorvastatin 80 mg versus rosuvastatin 40 mg[194]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	4/668 (0.6%)	1/668 (0.15%)	RR 4 (0.45 to 35.69)	4 more per 1000 (from 1 fewer to 52 more)	⊕⊕OO LOW	LESS IMPORTANT
Rhabdomyolysis – atorvastatin 40 mg versus rosuvastatin 20 mg[118]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/14 (0%)	0/20 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

[a]*The confidence interval of the estimate of effect crosses 2 default MIDs (0.75 and 1.25).*
[b]*The confidence interval of the estimate of effect crosses 1 default MID (1.25).*

11.4 Clinical evidence review for reduction in LDL cholesterol

LDL-cholesterol was included as an outcome in order to correlate statin LDL-cholesterol reduction with the outcomes of all-cause mortality, CV mortality, non-fatal MI and stroke. The specific aim was to correlate these outcomes with LDL-cholesterol reduction for individual statins and doses, thereby comparing the magnitude of high-intensity statin LDL-cholesterol lowering with the other statin intensities. Studies with ≥ 1 year follow-up were included rather than follow-ups of less than 1 year to facilitate the correlation. Table 51 details the final LDL-cholesterol values for statin versus placebo groups in the 16 studies reporting this outcome. Table 52 details the reported final LDL-cholesterol values for the 11 studies statin head to head studies.

Mean (SD) final LDL-cholesterol levels for each study are were meta-analysed according to statin intensity, statin type and dose, baseline and final placebo LDL cholesterol, mean LDL-cholesterol reduction and study follow-up (see Appendix I). Summary statistics for statin LDL-cholesterol reduction are given in Table 53, Table 54, Table 55, Table 56, Table 57, and Table 58.

Table 51: Final LDL-cholesterol levels in statin versus placebo studies

Study	Statin and dose	Intensity	Statin Final LDL cholesterol (mmol/litre) Mean (SD)	Placebo Final LDL cholesterol (mmol/litre) Mean (SD)	Follow-up time
Amarenco 2006[16] SPARCL	Atorvastatin 80 mg	High	1.89 (0.62)	3.32 (0.75)	Median 4.9 years
Anon 2002[9] ALLHAT-LLT	Pravastatin 40 mg	Low	4.77 (0.91)	5.32 (0.95)	Mean 4.8 years
Asselbergs 2004[24] PREVEND-IT	Pravastatin 40 mg	Low	3.1 (0.9)	3.9 (0.1)	Mean 46 months
Athyros 2002[25] GREACE	Atorvastatin 20 mg	High	2.51 (0.10)	4.37 (0.83)	Mean 3 years
Beishuizen 2005[28]	Simvastatin 20 mg	Medium	2.64 (0.96)	3.76 (0.83)	2 years
Byington 1995[43] PLAC II	Pravastatin 40 mg	Low	3.11 (0.59)	4.31 (0.56)	3 years
Colhoun 2004[53] CARDS	Atorvastatin 10 mg	Medium	2.11 (0.7)	3.12 (0.8)	Median 3.9 years
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg	High	2.46 (0.70)	2.84 (0.70)	Mean 51.5 months
Lemos 2013[142]	Rosuvastatin 10 mg	High	2.03 (1.15)	2.5 (0.70)	2 years
Sever 2003[234] ASCOT-LLA	Atorvastatin 10 mg	Medium	2.32 (0.72)	3.27 (0.81)	Median 3.3 years
Shukla 2005[239]	Atorvastatin 10 mg	Medium	1.91 (0.49)	2.25 (0.44)	1 year
Sola 2006[246]	Atorvastatin 20 mg	High	2.28 (0.94)	2.64 (0.87)	Mean 35 months
Teo 2000[259]	Simvastatin	Low	2.33 (0.49)	3.43 (0.56)	3-5 years

Study	Statin and dose	Intensity	Statin Final LDL cholesterol (mmol/litre) Mean (SD)	Placebo Final LDL cholesterol (mmol/litre) Mean (SD)	Follow-up time
SCAT	10 mg				
Terry 2007[260] CATZ	Simvastatin 80 mg	High	1.91 (0.49)	3.26 (0.49)	1 year
Yamada 2007[284]	Atorvastatin 10 mg	Medium	1.97 (0.47)	2.84 (0.91)	3 years
Yokoi 2005[285]	Pravastatin 20 mg	Low	2.98 (0.52)	3.64 (0.52	3 years

Table 52: Final LDL-cholesterol levels in head-to-head statin studies

Study	Statin 1: class	Statin 1: details	Statin 1: Final LDL cholesterol (mmol/litre) Mean (SD)	Statin 2: class	Statin 2: details	Statin 2: Final LDL cholesterol(mmol/litre) Mean (SD)	Follow-up time
Egede 2013[80] VIRHISTAMI	High	Rosuvastatin 5 mg/day	2.0 (0.4)	High	Rosuvastatin 40 mg/day	1.6 (0.7)	1 year
Gottlieb 2008[106]	Medium	Simvastatin 20 mg/day	2.63 (0.19)	High	Simvastatin 80 mg/day	2.32 (0.62)	1 year
Hong 2008[118]	High	Atorvastatin 40 mg/day	1.86 (0.67)	High	Rosuvastatin 20 mg/day	1.68 (0.64)	1 year
Hong 2009[117]	Medium	Simvastatin 10 mg/day	2.01 (0.52)	High	Rosuvastatin 10 mg/day	1.66 (0.54)	1 year
Nicholls 2011[194] SATURN	High	Atorvastatin 80 mg/day	1.82 (0.59)	High	Rosuvastatin 40 mg/day	1.62 (0.59)	2 years
Nissen 2005[196-198] REVERSAL	Low	Pravastatin 40 mg/day	2.85 (0.67)	High	Atorvastatin 80 mg/day	2.04 (0.78)	1.5 years
Pedersen 2005[206] IDEAL	Medium	Simvastatin 20 mg/day, Simvastatin 40 mg/day (23%)	2.58 (0.52)	High	Atorvastatin 80 mg/day	2.09 (0.52)	4.8 years
Raggi 2005[214]	Low	Pravastatin 40 mg/day	3.34 (0.80)	High	Atorvastatin 80 mg/day	2.38 (0.93)	1 year
Satoh 2009[229]	Low	Pravastatin 10 mg/day	2.90 (0.74)	Medium	Atorvastatin 10 mg/day	2.56 (0.72)	1 year
Schmermund 2006[232]	Medium	Atorvastatin 10 mg/day	2.82 (0.72)	High	Atorvastatin 80 mg/day	2.25 (0.86)	1 year
Zou 2003[292]	Low	Simvastatin 10 mg/day	3.03 (0.53)	Medium	Simvastatin 20 mg/day	2.83 (0.75)	1 year

Table 53: Statin versus placebo mean LDL-cholesterol reduction by statin intensity

Study	Statin and dose	Intensity	Final LDL cholesterol (mmol/litre) Mean difference (95%CI)*	Number of studies
Anon 2002[9] ALLHAT-LLT	Pravastatin 40 mg	Low	0.65 (0.620 to 0.68)	5
Asselbergs 2004[24] PREVEND-IT	Pravastatin 40 mg			
Byington 1995[43] PLAC II	Pravastatin 40 mg			
Teo 2000[259] SCAT	Simvastatin 10 mg			
Yokoi 2005[285]	Pravastatin 40 mg			
Beishuizen 2005[28]	Simvastatin 20 mg	Medium	0.99 (0.95 to 1.01)	5
Colhoun 2004[53] CARDS	Atorvastatin 10 mg			
Sever 2003[234] ASCOT-LLA	Atorvastatin 10 mg			
Shukla 2005[239]	Atorvastatin 10 mg			
Yamada 2007[284]	Atorvastatin 10 mg			
Amarenco 2006[16]	Atorvastatin 80 mg	High	1.26 (1.23 to 1.29)	6
Athyros 2002[25] GREACE	Atorvastatin 20 mg			
Koren 2004[133] ALLIANCE	Atorvastatin 80 mg			
Lemos 2013[142]	Rosuvastatin 10 mg			
Sola 2006[246]	Atorvastatin 20 mg			
Terry 2007[260] CATZ	Simvastatin 80 mg			

**Results presented are summary statistics and it should be noted that absolute difference in LDL-cholesterol is dependent on both statin intensity and baseline LDL cholesterol.*

Table 54: Statin versus placebo mean LDL-cholesterol reduction by statin and dose

Statin and dose	Study	Intensity	Final LDL cholesterol (mmol/litre) Mean difference (95%CI)	Number of studies
Atorvastatin 10 mg	Colhoun 2004[53] CARDS Sever 2003[234] ASCOT-LLA, Shukla 2005[239], Yamada 2007[284]	Medium	0.98 (0.95 to 1.00)	4
Atorvastatin 20 mg	Athyros 2002[25] GREACE, Sola 2006[246]	High	1.70 (1.65 to 1.75)	2
Atorvastatin 80 mg	Amarenco 2006[16], Koren 2004[133] ALLIANCE	High	1.10 (1.13 to 1.06)	2
Pravastatin 20 mg	Yokoi 2005[285]	Low	0.66 (0.54 to 0.78)	1
Pravastatin 40 mg	Anon 2002[9] ALLHAT-LLT, Asselbergs 2004[24] PREVEND-IT, Byington 1995[43]	Low	0.59 (0.56 to 0.63)	3

Statin and dose	Study	Intensity	Final LDL cholesterol (mmol/litre) Mean difference (95%CI)	Number of studies
	PLAC II			
Rosuvastatin 10 mg	Lemos 2013[142]	High	0.43 (0.12 to 0.97)	1
Simvastatin 10 mg	Teo 2000[259] SCAT	Low	1.10 (1.00 to 1.20)	1
Simvastatin 20 mg	Beishuizen 2005[28]	Medium	1.12 0.90 to 1.34)	1
Simvastatin 80 mg	Terry 2007[260] CATZ	High	1.35 (1.14 to 1.56)	1

Table 55: High-intensity versus low-intensity statin mean LDL-cholesterol reduction

Study	Statin 1: intensity	Statin 2: details	Statin 1: intensity	Statin 2: details	Final LDL cholesterol (mmol/litre) Mean difference (95% CI)
Nissen 2005[196-198] REVERSAL	Low	Pravastatin 40 mg/day	High	Atorvastatin 80 mg/day	0.88 (0.73 to 1.02)
Raggi 2005[214]	Low	Pravastatin 40 mg/day	High	Atorvastatin 80 mg/day	

Table 56: High-intensity versus medium-intensity statin mean LDL-cholesterol reduction

Study	Statin 1: intensity	Statin 2: details	Statin 1: intensity	Statin 2: details	Final LDL cholesterol (mmol/litre) Mean difference (95% CI)
Gottlieb 2008[106]	Medium-intensity statin	Simvastatin 20 mg/day	High-intensity statin	Simvastatin 80 mg/day	0.48 (0.40 to 0.55)
Hong 2009[117]	Medium-intensity statin	Simvastatin 20 mg/day	High-intensity statin	Rosuvastatin 10 mg/day	
Pedersen 2005[206] IDEAL	Medium-intensity statin	Simvastatin 20 mg/day	High-intensity statin	Atorvastatin 80 mg/day	
Schmermund 2006[232]	Low-intensity statin	Atorvastatin 10 mg/day	High-intensity statin	Atorvastatin 80 mg/day	

Table 57: Medium-intensity versus low-intensity statin mean LDL-cholesterol reduction

Study	Statin 1: intensity	Statin 2: details	Statin 1: intensity	Statin 2: details	Final LDL cholesterol (mmol/litre) Mean difference (95% CI)
Satoh 2009[229]	Low-intensity statin	Pravastatin 10 mg/day	Medium-intensity statin	Atorvastatin 10 mg/day	0.24 (0.09 to 0.39)
Zou 2003[292]	Low-intensity statin	Simvastatin 10 mg/day	Medium-intensity statin	Simvastatin 20 mg/day	

Table 58: High-intensity versus high-intensity statin mean LDL-cholesterol reduction

Study	Statin 1: intensity	Statin 2: details	Statin 1: intensity	Statin 2: details	Final LDL cholesterol (mmol/litre) Mean difference (95% CI)
Egede 2013[80] VIRHISTAMI	High-intensity statin	Rosuvastatin 40 mg/day	High-intensity statin	Rosuvastatin 5 mg/day	0.23 (0.12 to 0.35)
Hong 2008[118]	High-intensity statin	Atorvastatin 40 mg/day	High-intensity statin	Rosuvastatin 20 mg/day	
Nicholls 2011[194] SATURN	High-intensity statin	Atorvastatin 80 mg/day	High-intensity statin	Rosuvastatin 40 mg/day	
Zou 2003[292]	Low-intensity statin	Simvastatin 10 mg/day	Medium-intensity statin	Simvastatin 20 mg/day	

11.5 Number needed to treat

The GDG requested available information on NNT and NNH from the clinical trial evidence. NNT can be calculated for single studies from the risk difference (RD) as NNT = 1/[RD]. To calculate NNT from the results of a meta-analysis of risk ratios, assumed control risk (ACR) is required and it would usually be appropriate to do this for a range of different ACRs. NNTs are affected by variations in risk differences in studies, baseline event rates in control groups, differences in clinical setting and duration of follow up. The studies included in the guideline meta-analyses vary in these characteristics.

A recent Cochrane systematic review identified 18 RCTs on statin therapy versus placebo or control in primary prevention[258]. The number of participants was 56,934 (60.3% men, 39.7% women), and the studies were conducted between 1994 and 2008. The median level of CVD risk in the control group was 15% over 10 years. Table 59 details the NNTs for all-cause mortality, CVD outcomes and diabetes over 5 years. The review reported that rates of overall adverse events (17%) and stopping treatment (12%) were similar in the 2 groups. The incidence of myalgia, rhabdomyolysis, liver, enzyme elevation and renal dysfunction did not differ between the groups. The authors concluded that the benefits of statins in primary prevention outweigh the risks of serious life threatening illness.

Table 59: NNT and statins for primary prevention. Adapted from FC Taylor, M Huffman, S Ebrahim, Statin Therapy for Primary Prevention of Cardiovascular Disease. JAMA. 2013;310(22):2451-2452

Outcome	Number of RCTs	NNT 5 years	95%CI
All-cause mortality	13	138	92 to 321
Total CVD events	9	49	40 to 66
Total CHD events	14	88	72 to 119
Total stroke	10	155	106 to 309
Revascularisation	7	96	78 to 129
Type 2 diabetes	2	99[(a)]	46 to 1778

(a) NNH

11.6 Economic evidence

11.6.1 Published literature

Six economic evaluations were included that compared statins with either placebo or statins. Four papers, relating to 3 studies evaluated statins in adults without established CVD (primary prevention),[50,164,268,269] 5 papers, relating to 3 studies evaluated statins in adults with established CVD (secondary prevention)[21,22,176,268,269] (1 study covered both), and 1 paper evaluated statins in people with chronic kidney disease.[86] These are summarised in the economic evidence profiles below (Table 60–Table 64) and the economic evidence tables in Appendix H. No relevant economic evaluations were identified that compared statins with either placebo or statins in people with type 1 diabetes or type 2 diabetes.

One hundred and twenty-one further papers relating to this review question were identified but were excluded due to limited applicability, methodological limitations or the availability of more applicable evidence. These are listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 60: Economic evidence profile: statins versus placebo for primary prevention in adults without CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Ward 2005[268,269] (UK) – conducted for NICE technology appraisal 94[182]	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis • Intervention: statins (as a single class) versus placebo • Effectiveness: taken from a meta-analysis of 48 trials • Annual statin costs: £317 (weighted average of 2004 UK costs) • Time horizon: lifetime • Cost year: 2004 (UK)	Not reported	Not reported	ICER: £11,200 per QALY gained (Men, starting age 65, 1.5% annual CHD risk, 2.4% annual CVD risk)	ICERs increase with increasing starting age and decreasing CHD/CVD risk level, and are above £20,000 per QALY gained for men and women aged 85 at 1.5% CHD risk and men aged 85 at 2.0% CHD risk. Sensitivity analyses indicate that the results are likely to be sensitive to discount rates of 3.5% for cost and benefits and a reduced duration of effectiveness of statins (10 years)
McConnachie 2014[163] (UK)	Directly applicable [(c)]	Minor limitations [(d)]	• Cost–utility analysis • Intervention: pravastatin 40 mg for 5 years versus placebo, followed up for a further 10 years (with similar statin usage in both arms after end of trial) • Effectiveness: taken from WOSCOPS trial[237] (UK) with 10 years further follow-up hospital admissions data from linked NHS health records • Annual statin costs: used the cost of pravastatin 40 mg (£36), similar to current UK cost (£23) • Follow up: 15 years • Cost year: 2012 (UK)	−£710	0.136 QALYs	5-year statin treatment is dominant	95% CI for cost saving per person: −£1090 to −£320. 95% CI for QALYs gained per person: 0.025 to 0.247. 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.

Abbreviations: 95% CI: 95% confidence interval; CHD: coronary heart disease; CVD: cardiovascular disease; QALY: quality-adjusted life year

(a) 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.
(b) 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 risk threshold for treatment for primary prevention.
(c) Looks at Scottish men aged 45–54 at start. Follows NICE reference case where possible. Utility values taken from Ward.
(d) 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.

Table 61: Economic evidence profile: statins versus placebo for primary prevention in adults without CVD, with low LDL cholesterol and high high-sensitivity C-reactive protein

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Choudhry 2011[49] (USA)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis • Population: men ≥50 and women ≥60 with LDL cholesterol <3.36 mmol/litre • Intervention: rosuvastatin 20 mg for those with hs-CRP ≥2.0 mg/litre versus usual care • Effectiveness: taken from JUPITER trial[222] • Annual statin costs: £866 used for first 7 years, reducing to £239 after 8 years (assumed cost after rosuvastatin comes off patent). Current UK cost: £339 • Time horizon: lifetime • Cost year: 2009 (US) [(c)]	£5161	0.31 QALYs	ICER: £16,465 per QALY gained	ICER for probabilistic results: £18,018 per QALY gained (95% CI: £6796 to £41,024). The ICER was above £20,000 per QALY in sensitivity analyses where statins were less effective, had higher rates of adverse events, treatment effect lasts only 15 years, a disutility of 0.02 is added for statin use, or Framingham CV risk is <10% (unless statin cost is also <£350/year).

Abbreviations: 95% CI: 95% confidence interval; hs-CRP: high-sensitivity C-reactive protein; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
(a) Based on a population with low CV risk but high levels of hs-CRP. 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 US healthcare system.

(b) 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.

(c) Converted using 2009 purchasing power parities.[204]

Table 62: Economic evidence profile: statins versus placebo for secondary prevention in adults with CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Ward 2005[268,269] (UK) – conducted for NICE technology appraisal 94[182]	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis • Intervention: statins (as a single class) versus placebo • Effectiveness: taken from a meta-analysis of 48 trials • Annual statin costs: £317 (weighted average of 2004 UK costs) • Time horizon: lifetime • Cost year: 2004 (UK)	£3218	0.314 QALY	ICER: £9100 per QALY gained (Men, starting age 65)	ICERs are below £20,000 for all age and sex subgroups. Sensitivity analyses indicate that the results are likely to be sensitive to discount rates of 3.5% for cost and benefits and a reduced duration of effectiveness of statins (10 years)

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) 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.

(b) 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.

Table 63: Economic evidence profile: high intensity statins versus medium intensity statins for secondary prevention in adults with CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NCCPC 2008[176]	Directly applicable [(a)]	Potentially serious	• Cost–utility analysis • Intervention: high-intensity	ACS:	ACS:	ICERs: ACS:	Both conclusions (high-intensity statins are cost effective at a

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
(UK) – conducted for NICE clinical guideline 67[177]		limitations [(b)]	statins (atorvastatin 80 mg) versus lower-intensity statins (simvastatin 20 mg, atorvastatin 10 mg or pravastatin 40 mg) for people with either ACS or CHD • Effectiveness: meta-analysis of 4 head-to-head trials[44,62,140,206] • Annual statin costs: UK 2008 costs – atorvastatin 80 mg: £368, simvastatin 80 mg: £65 • Time horizon: lifetime • Cost year: 2008 (UK)	£1418 CHD: £2389	0.32 QALYs CHD: 0.08 QALYs	£4397 per QALY gained CHD: £28,361 per QALY gained	threshold of £20,000 per QALY for ACS but not for CHD) were robust to one-way sensitivity analyses varying effectiveness of treatment, 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.
Ara 2009[21,22]	Directly applicable [(c)]	Potentially serious limitations [(d)]	• Cost–utility analysis • Intervention: simvastatin 80 mg (S80), atorvastatin 80 mg (A80) or rosuvastatin 40 mg (R40) (all high intensity) versus simvastatin 40 mg (S40, medium intensity), for people with recent ACS • Effectiveness: taken from a network meta-analysis of 28 trials of statin effectiveness in reducing LDL cholesterol, converted to reductions in CV events using CTT 2005[26] • Annual statin costs: UK 2008 costs (S40: £17, S80: £34, R40: £387), with A80 projected to be £92 [(e)] • Time horizon: lifetime	S80−S40: £588 A80−S40: NR [(f)] R40−S40: £3941	S80−S40: 0.111 QALYs A80−S40: NR [(f)] R40−S40: 0.316	ICERs: S80−S40: £5319 per QALY gained A80−S40: £3172 per QALY gained R40−S40: £12,484 per QALY gained A80−S80: A80 dominates S80 (is less costly and more effective)	In the base case scenario in the paper[(e)] the conclusion was found to be robust to all sensitivity analyses apart from when the relative clinical effectiveness of medium and high intensity statins are varied. These sensitivity analyses were not carried out relating to the scenario with lower-cost (£92 per year) A80. Different assumptions regarding adherence to statins were also studied, but these also had only moderate effect on cost effectiveness, both in the base case and for lower-cost A80 – with the ICER for A80 versus S40 varying between £3155 and £7331

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Cost year: 2007 (UK)			R40−A80: ICER NR, but A80 is stated as the preferred, cost-effective treatment at a threshold of £20,000 per QALY gained	dependent on the pattern of adherence. The analysis was also repeated with a third, lower possible A80 cost of £21 per year. The ICER was not stated, but at this cost A80 was the preferred, cost-effective intervention at all cost-effectiveness thresholds

Abbreviations: ACS: acute coronary syndrome; CHD: coronary heart disease; CV: cardiovascular; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) Designed in accordance with NICE reference case.

(b) 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 (CAD) secondary prevention patients.

(c) Based on UK ACS population, following NICE reference case.

(d) 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.

(e) The papers examined a base case using the then current (branded) atorvastatin 80 mg price of £368 per year, but conducted a sensitivity analysis using potential future annual generic costs of £92 – it is this sensitivity analysis which is summarised in this table.

(f) Incremental costs and outcomes and ICERs are given for the base case (in which all high-intensity statins are cost effective compared to simvastatin 40 mg at a cost-effectiveness threshold of £20,000 per QALY gained, but with rosuvastatin 40 mg dominating atorvastatin 80 mg and being cost effective compared to simvastatin 80 mg), but not for the sensitivity analyses with lower-priced atorvastatin.

Table 64: Economic evidence profile: statins versus placebo in adults with CKD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Erickson 2013[86] (USA)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Cost–utility analysis • Intervention: statins as a single class • Effectiveness: taken from	£1244	0.10 QALYs	ICER: £12,440 per QALY gained	Base case related to men aged 65. For women aged 65 ICER=£23,084. Treatment is cost effective at a threshold of £34,556 in 99% of probabilistic simulations for men

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			Cochrane meta-analysis[193] • Statin costs: used the cost of pravastatin 40 mg (£33), similar to current UK costs • Time horizon: lifetime • Cost year: 2010 (US) (c)				aged 65 or 50 and 94% for women aged 65, but 38% for women aged 50. 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. If statins slow CKD progression as well as CVD progression then they would be cost saving.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) 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.

(b) 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.

(c) Converted using 2010 purchasing power parities. [204]

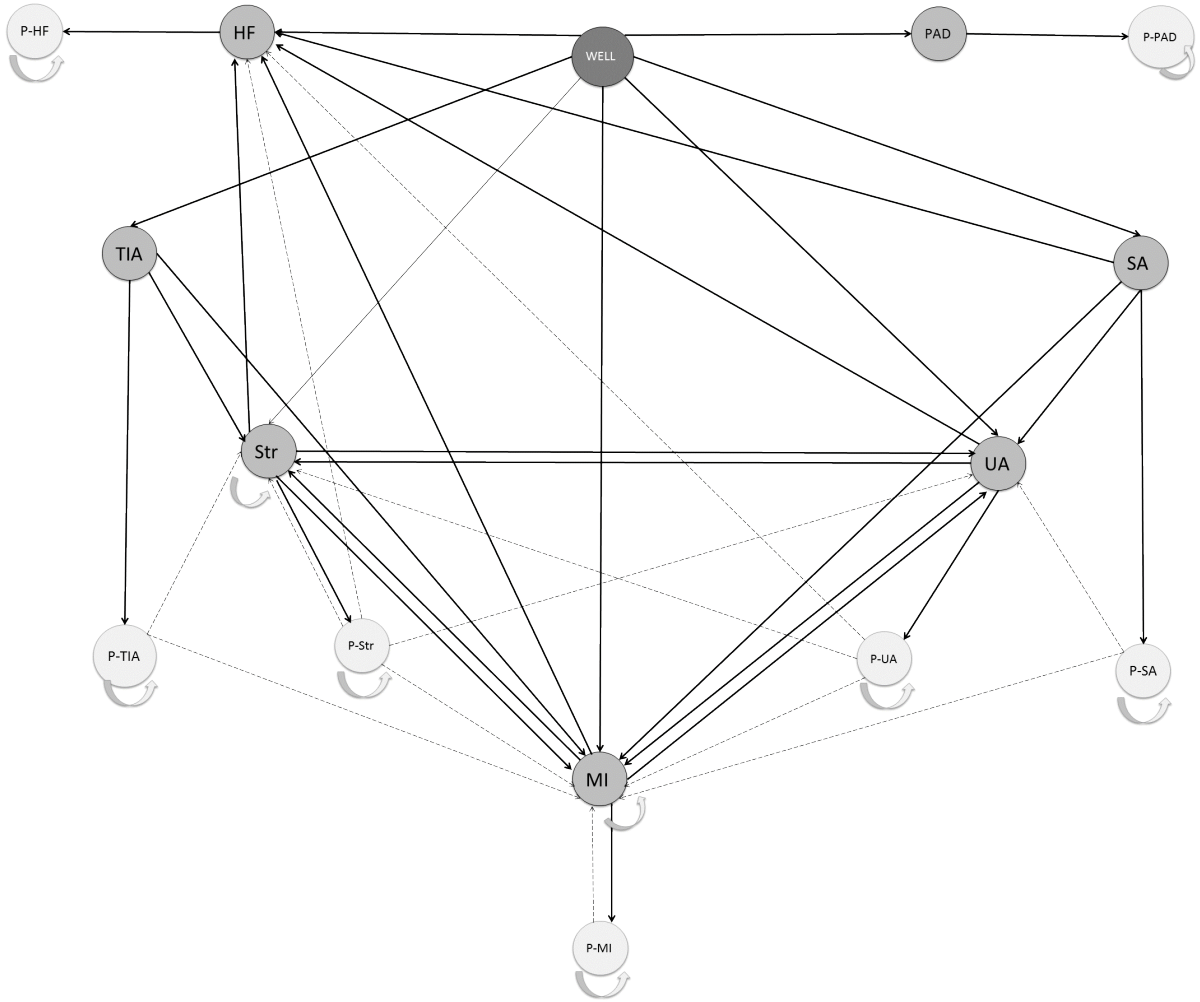
11.6.2 New cost-effectiveness analysis

Original cost-effectiveness modelling was undertaken for this question. A summary is included here. Evidence statements summarising the results of the analysis can be found in Section 11.7 below. The full analysis can be found in Appendix L.

11.6.2.1 Structure

Two health economic models were developed, following the NICE reference case[191] and drawing on models created by Ward et al.[268,269] which informed NICE Technical appraisal 94,[182] and by the NCCPC[173] as part of Clinical guideline 67,[177] both of which this guideline updates. The first model is a health state transition (Markov) model to investigate the secondary prevention of CVD. The second Markov model includes the same structure for secondary prevention but adds an initial primary prevention phase.

Figure 8: Structure of the health economic models for the cost effectiveness of statins



Abbreviations: 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 both the primary 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 a further CV event.

A cohort of individuals with defined age and gender moves through each model in annual cycles during each of which they may experience a CV event, dependent on defined transition probabilities which vary according to age. Each health state in the model is associated with an annual cost of treatment and a utility multiplier to represent the quality of life for people in that state. The base case analyses investigate males aged 60 at the start of the model. All cohort members are followed until death or age 100 years. The costs of both statin treatment and treatment for CV events experienced by cohort members are discounted at an annual rate of 3.5% and summed over the lifetime. The quality of life of cohort members is also discounted at an annual rate of 3.5% and summed over the lifetime. These are used to calculate incremental cost-effectiveness ratios (ICERs) and net health benefit (NHB) comparing the different treatment options.

The 4 interventions modelled were those listed in the protocol for the clinical review in this chapter (see Table 37 and Table 38 for details of which statins are grouped in each class):

- placebo or no treatment
- low-intensity statins
- medium-intensity statins
- high-intensity statins.

The risk ratios found in the meta-analyses performed for the clinical review (Table 41) were applied to baseline event rates taken from Ward 2005[263] and NCCPC 2008.[173] Utility multipliers for each health state were also taken from these previous models. The costs of each health state were calculated based on assumed typical resource use.

The results of these models investigated the cost effectiveness of

- Secondary prevention for people with existing CVD, using the secondary model.
- Primary prevention for people without existing CVD and without diabetes, using the primary model, calibrated to relate to CV risk as predicted by the QRISK2 tool.
- Primary prevention for people without existing CVD but with type 2 diabetes, using the primary model, calibrated to relate to CV risk as predicted by the UKPDS tool.

The analysis using the primary model was carried out twice because the different risk tools assess different components of CV risk (QRISK2 predicts the risk of fatal or non-fatal angina, MI, TIA or stroke; UKPDS predicts the risk of fatal or non-fatal MI or stroke). The risk scores given by the 2 tools are hence not equivalent. The model assumed the same distribution of CV events in people with type 2 diabetes as in the general primary prevention population, and assumed that statins would have the same magnitude of effect in reducing CV events in both populations, in line with the clinical review.

Separate analyses were not carried out for people with type 1 diabetes or chronic kidney disease, because the clinical review found no evidence to justify a different effectiveness of statin therapy in these groups, and because no alternative risk tool was recommended that is specific to these groups.

To account for the finding of increased rates of type 2 diabetes in people taking statins, additional costs were added to the model to represent the costs of treating cases of diabetes which may be diagnosed 4 years earlier than would have been the case without the use of statins. Quality of life was also decreased in line with the rates of complications for people with diabetes. In sensitivity analyses costs were further increased to cover the full lifetime cost of diabetes treatment in the case that all excess cases of diabetes diagnoses when undergoing statin treatment are additional cases which would not otherwise have occurred, rather than just being existing cases brought forward. Sensitivity analyses also investigated the impact on cost effectiveness if up to 20% of people stopped taking a high-intensity statin or changed to a lower-intensity statin as a result of adverse events.

11.6.2.2 Assumptions

The models rely on the standard assumptions of Markov models: that only 1 event can occur in any cycle (1 year), and that there is no memory of which events have happened previously. Thus, for example, the probability of a further stroke for someone in the post-stroke state is the same regardless of if they have had 1 or several previous strokes.

It is assumed that the risk ratios given for treatment with each class of statins are constant regardless of the baseline CV risk – that is, someone with low CV risk will receive the same proportional reduction in that risk as would someone with a high CV risk. This is unproven, but is consistent with the results of meta-analysis carried out by the Cholesterol Treatment Trialists, which found effectiveness to be broadly similar for those at different risk levels.[166] It is also assumed that these risk ratios are constant regardless of baseline LDL-cholesterol levels. It is not known whether this is in fact the case. It is assumed that all adverse events other than the advanced onset of diabetes are temporary and reversible, and so the impact they will have is that those experiencing these adverse events would cease taking statins or change to an alternative statin. This is the case for myalgia and liver adverse events. Rhabdomyolysis may lead to lasting impacts on health, including death, but true rhabdomyolysis is sufficiently rare that including it in the model would not make an appreciable impact in terms of costs or benefits per person.

11.6.2.3 Summary of results

Secondary prevention

The analysis found 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 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.

Primary prevention

The analysis found 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

£3438 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 age and sex subgroups and almost all sensitivity analyses.

These results do not include the potential effects of adverse events other 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.

Type 2 diabetes

The analysis found 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 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 £3445 per QAly gained compared with simvastatin 20 mg.

11.7 Evidence statements

11.7.1 Clinical

Evidence statements are given for individual outcomes. The effect size estimate may be too small to be clinically important for an individual outcome; however total reduction of all CV outcomes may be of greater magnitude.

Statin versus placebo, subgroup analysis by statin intensity

All-cause mortality

- High quality evidence showed that statins are more effective when compared to placebo at reducing all-cause mortality at up to 6 years, but the effect size is too small to be clinically important [26 studies, n=120,329].
- High quality evidence showed that low-intensity statins are more effective when compared to placebo at reducing all-cause mortality at up to 6 years, but the effect size is too small to be clinically important [12 studies, n=48,978].
- High quality evidence showed that medium-intensity statins are more effective when compared to placebo at reducing all-cause mortality at up to 5 years, but the effect size is too small to be clinically important [8 studies, n=42,687].
- High quality evidence showed that high-intensity statins are more effective when compared to placebo at reducing all-cause mortality at up to 5 years, but the effect size is too small to be clinically important [6 studies, n=27,664].

CV mortality

- High quality evidence showed that statins are more effective when compared to placebo at reducing CV mortality at up to 6 years, but the effect size is too small to be clinically important [22 studies, n=118,938].
- High quality evidence showed that low-intensity statins are more effective when compared to placebo at reducing CV mortality at up to 6 years, but the effect size is too small to be clinically important [11 studies, n=50,127].
- High quality evidence showed that medium-intensity statins are more effective when compared to placebo at reducing CV mortality at up to 5 years, but the effect size is too small to be clinically important [7 studies, n=42,248].
- Moderate quality evidence showed that high-intensity statins are more effective when compared to placebo at reducing CV mortality at up to 6 years, but the effect size is too small to be clinically important at up to 5 years, but the effect size is too small to be clinically important [4 studies, n=26,576].

Non-fatal MI

- Moderate quality evidence showed that statins are more clinically more effective when compared to placebo at reducing non-fatal MI at up to 6 years [21 studies, n=91,482].
- Moderate quality evidence suggested that there may be no clinical difference between low-intensity statins when compared placebo at reducing non-fatal MI at up to 6 years, but the direction of the estimate of effect favoured low-intensity statins [13 studies, n=40,589].
- High quality evidence showed that medium-intensity statins are more clinically more effective when compared to placebo at reducing non-fatal MI at up to 5 years [4 studies, n=28,068].
- High quality evidence showed that high-intensity statins are more clinically more effective when compared to placebo at reducing non-fatal MI at up to 5 years [4 studies, n=22,825].

Stroke

- Moderate quality evidence suggested that there may be no clinical difference between statins when compared to placebo at reducing stroke at up to 6 years, but the direction of the estimate of effect favoured statins [19 studies, n=109,244].
- High quality evidence showed that low-intensity statins are more effective when compared to placebo at reducing stroke at up to 6 years, but the effect size is too small to be clinically important [10 studies, n=44,310].
- Moderate quality evidence suggested that medium-intensity statins are potentially more effective when compared to placebo at reducing stroke at up to 5 years [5 studies, n=38,350].
- Moderate quality evidence suggested that there may be no clinical difference between high-intensity statins when compared to placebo at reducing stroke at up to 5 years, but the direction of the estimate of effect favoured high-intensity statins [4 studies, n=26,575].

Myalgia

- High evidence showed that there is no clinical difference between statins and placebo in causing myalgia at up to 5 years [9 studies, n=29,480].
- Moderate quality evidence suggested that there may be no clinical difference between low-intensity statins when compared to placebo in causing myalgia at up to 5 years, but the direction of the estimate of effect favoured low-intensity statins [3 studies, n=16,670].
- Low quality evidence suggested that there may be no clinical difference between medium-intensity statins when compared to placebo in causing myalgia at up to 5 years, but the direction of the estimate of effect favoured placebo [3 studies, n=5498].

- High quality evidence showed that there is no clinical difference between high-intensity statins and placebo in causing myalgia at up to 5 years [3 studies, n=7312].

Liver adverse events (transaminases more than 3 times the upper limit of normal)

- High quality evidence showed that statins when compared to placebo cause more liver adverse events at up to 5 years [16 studies, n=84,969].
- Moderate quality evidence showed that low-intensity statins when compared to placebo cause more liver adverse events at up to 5 years [6 studies, n=32,273].
- Moderate quality evidence suggested that medium-intensity statins when compared to placebo cause more liver adverse events at up to 5 years [6 studies, n=27,582]
- Moderate quality evidence showed that high-intensity statins when compared to placebo cause more liver adverse events at up to 5 years [4 studies, n=25,114].

New-onset diabetes

- Moderate quality evidence showed that statins when compared to placebo cause more new-onset diabetes at up to 6 years, but the effect size is too small to be clinically important [10 studies, n=78,017].
- Moderate quality evidence showed that low-intensity statins when compared to placebo cause more new-onset diabetes at up to 6 years, but the effect size is too small to be clinically important [6 studies, n=33,627].
- High quality evidence showed that medium-intensity statins when compared to placebo cause more new-onset diabetes at up to 5 years, but the effect size is too small to be clinically important [3 studies, n=26,588].
- Moderate quality evidence suggested that there may be no clinical difference between placebo and high-intensity statins in causing new-onset diabetes at 2 years, but the direction of the estimate of effect favoured placebo [1 study, n=17,802].

Rhabdomyolysis

- Low quality evidence suggested that there may be no clinical difference statins and placebo in causing rhabdomyolysis at up to 5 years, but the direction of the estimate of effect could favour either intervention [16 studies, n=75,828].
- Low quality evidence suggested that low-intensity statin when compared to placebo caused fewer rhabdomyolysis events at up to 4 years, but the direction of the estimate of effect could favour either intervention [3 studies, n=6737].
- Moderate quality evidence suggested that medium-intensity statins when compared to placebo caused fewer rhabdomyolysis events at up to 5 years [9 studies, n=8603].
- Low quality evidence suggested that high-intensity statin when compared to placebo caused fewer rhabdomyolysis events at up to 5 years, but the direction of the estimate of effect could favour either intervention [4 studies, n=25,965].

Statin versus placebo, subgroup analysis by strata

All-cause mortality

- High quality evidence showed that statins are more effective when compared to placebo at reducing all-cause mortality in people with CVD at up to 6 years, but the effect size is too small to be clinically important [15 studies, n=60,106].
- High quality evidence showed that statins are more effective when compared to placebo at reducing all-cause mortality in people without CVD at up to 5 years, but the effect size is too small to be clinically important [8 studies, n=54,665].

- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo at reducing all-cause mortality in people with type 2 diabetes at up to 5 years, but the direction of the estimate of effect favoured statins [4 studies, n=5700].
- Low quality evidence suggested that there may be no clinical difference between statins when compared to placebo at reducing all-cause mortality in people with CKD at up to 5 years, but the direction of the estimate of effect favoured statins [2 studies, n=4978].

CV mortality

- High quality evidence showed that statins are more effective when compared to placebo at reducing CV in people with CVD at up to 6 years, but the effect size is too small to be clinically important [14 studies, n=59,949].
- High quality evidence showed that statins are more effective when compared to placebo at reducing CV mortality in people without CVD at up to 5 years, but the effect size is too small to be clinically important [5 studies, n=52,889].
- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo at CV mortality in people with type 2 diabetes at up to 5 years, but the direction of the estimate of effect favoured statins [4 studies, n=6036].
- Moderate quality evidence suggested that placebo is potentially more clinically effective when compared to statins at reducing CV mortality in people with CKD at up to 5 years [2 studies, n=1007].

Non-fatal MI

- Moderate quality evidence showed that statins are more clinically effective when compared to placebo at reducing non-fatal MI in people with CVD at up to 6 years [13 studies, n=54,015].
- High quality evidence showed that statins are more clinically effective when compared to placebo at reducing non-fatal MI in people without CVD at up to 5 years [5 studies, n=33,515].
- Low quality evidence suggested that statin is potentially more clinically effective when compared to placebo at reducing non-fatal MI in people with type 2 diabetes at up to 5 years [4 studies, n=3876].
- Moderate quality evidence suggested that statin is potentially more clinically effective when compared to placebo at reducing non-fatal MI in people with CKD at up to 5 years [3 studies, n=5842].

Stroke

- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo at reducing stroke in people with CVD at up to 6 years, but the direction of the estimate of effect favoured statins [11 studies, n=54,426].
- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo at reducing stroke in people without CVD at up to 5 years, but the direction of the estimate of effect favoured statins [6 studies, n=53,116].
- Moderate quality evidence suggested that statins are potentially more clinically effective when compared to statins at reducing stroke in people with type 2 diabetes at up to 5 years [4 studies, n=10 464].,
- Moderate quality evidence suggested that statins are potentially more clinically effective when compared to placebo at reducing stroke in people with CKD at up to 5 years [4 studies, n=5985].

Myalgia

- High evidence showed that there is no clinical difference between statins and placebo in causing myalgia in people with CVD at up to 6 years [4 studies, n=16,406].

- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo in causing myalgia in people without CVD at up to 5 years, but the direction of the estimate of effect favoured placebo [2 studies, n=7576].
- Moderate evidence suggested that there may be no clinical difference between statins when compared to placebo in causing myalgia in people with type 2 diabetes at up to 5 years, but the direction of the estimate of effect favoured placebo [3 studies, n=5498].
- High evidence showed that there is no clinical difference between statins and placebo in causing myalgia in people with CKD at up to 5 years [1 studies, n=3267].

Liver adverse events (transaminases more than 3 times the upper limit of normal)

- Moderate quality evidence showed that statins when compared to placebo cause more liver adverse events in people with CVD at up to 6 years [9 studies, n=43,063].
- Moderate quality evidence showed that statins when compared to placebo cause more liver adverse events in people without CVD at up to 5 years [5 studies, n=35,960].
- Moderate quality evidence suggested that statins when compared to placebo cause more liver adverse events in people with type 2 diabetes at up to 5 years [4 studies, n=11,461].
- Low quality evidence suggested that there may be no clinical difference between statins and placebo in causing liver adverse events in people with CKD at up to 5 years, but the direction of the estimate of effect could favour either intervention 3 studies, n=5426].

New-onset diabetes

- High evidence showed that there is no clinical difference between statins and placebo in causing new onset diabetes in people with CVD at up to 6 years [5 studies, n=34,295].
- High quality evidence showed that statins when compared to placebo cause more new onset diabetes in people without CVD at up to 5 years, but the effect size is too small to be clinically important [5 studies, n=43,722].

Rhabdomyolysis

- Moderate quality evidence suggested that statins when compared to placebo cause more rhabdomyolysis events in people with CVD at up to 6 years, but the direction of the estimate of effect could favour either intervention [7 studies, n=39,999].
- Low quality evidence suggested that there may be no clinical difference between statins and placebo in causing rhabdomyolysis events at up to 5 years in people without CVD, but the direction of the estimate of effect could favour either intervention [5 studies, n=16,583].
- Low quality evidence suggested that statins when compared to placebo cause more rhabdomyolysis events in people with type 2 diabetes at up to 5 years, but the direction of the estimate of effect could favour either intervention [4 studies, n=11,461].
- Moderate quality evidence suggested that statins when compared to placebo cause more rhabdomyolysis events in people with CKD at up to 5 years [3 studies, n=5426].

Head-to-head statin studies

<u>High intensity versus low-intensity statin</u>

Atorvastatin 80 mg versus pravastatin 40 mg

All-cause mortality

- Low quality evidence showed that atorvastatin 80 mg is potentially more clinically effective when compared to pravastatin 40 mg at reducing all-cause mortality at up to 2 years [2 studies, n=5053].

CV mortality

- Moderate quality evidence showed that atorvastatin 80 mg is potentially more clinically effective when compared to pravastatin 40 mg at reducing CV mortality at up to 2 years [2 studies, n=5053].

Non-fatal MI

- Moderate quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg when compared to pravastatin 40 mg at reducing non-fatal MI at 2 years, but the direction of the estimate of effect favoured atorvastatin 80 mg [1 study, n=4162].

Stroke

- Low quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg and pravastatin 40 mg at reducing stroke at 2 years, but the direction of the estimate of effect could favour either intervention [2 studies, n=5053].

Myalgia

- Low quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg and pravastatin 40 mg in causing myalgia at 1 year, but the direction of the estimate of effect could favour either intervention [1 study, n=891].

Rhabdomyolysis

- Very low quality evidence suggested that pravastatin 40 mg is potentially more clinically effective when compared to atorvastatin 80 mg in showing a reduced rate of rhabdomyolysis at 2 years [3 studies, n=5528].

Liver adverse events (transaminases more than 3 times the upper limit of normal)

- Moderate quality evidence showed that pravastatin 40 mg is more clinically effective when compared to atorvastatin 80 mg in showing reduced liver adverse events at up to 2 years [3 studies, n=5528].

High intensity versus medium-intensity statin

All-cause mortality

Combined studies

- High quality evidence showed that there is no clinical difference between high-intensity and medium-intensity statin at reducing all-cause mortality at up to 7 years [4 studies, n=35,105].

Atorvastatin 80 mg versus atorvastatin 10 mg

- High quality evidence suggested that there may be no clinical difference between atorvastatin 10 mg when compared to atorvastatin 80 mg at reducing all-cause mortality at up to 5 years, but the direction of the estimate of effect favoured atorvastatin 80 mg [1 study, n=6549].

People with CKD; atorvastatin 80 mg versus atorvastatin 10 mg

- High quality evidence showed that there is no clinical difference between atorvastatin 80 mg and atorvastatin 10 mg in people with CKD at reducing all-cause mortality at up to 5 years [1 study, n=3107].

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that there is no clinical difference between simvastatin 20 mg and atorvastatin 80 mg at reducing all-cause mortality at up to 5 years [1 study, n=8888].

Simvastatin 80 mg versus simvastatin 20 mg

- Moderate quality evidence showed that there is no clinical difference between simvastatin 20 mg and simvastatin 80 mg at reducing all-cause mortality at up to 7 years [2 studies, n=16,561].

CV mortality

Combined studies

- High quality evidence showed that there is no clinical difference between high-intensity and medium-intensity statin at reducing CV mortality at up to 7 years [4 studies, n=35,105].

Atorvastatin 80 mg versus atorvastatin 10 mg

- High quality evidence showed that there is no clinical difference between atorvastatin 10 mg and atorvastatin 80 mg at reducing CV mortality at up to 5 years [1 study, n=10,001].

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that there is no clinical difference between simvastatin 20 mg and atorvastatin 80 mg at reducing CV mortality at up to 5 years [1 study, n=8888].

Simvastatin 80 mg versus simvastatin 20 mg

- Moderate quality evidence showed that there is no clinical difference between simvastatin 20 mg and simvastatin 80 mg at reducing CV mortality at up to 7 years [2 studies, n=16,561].

Non-fatal MI

Combined studies

- High quality evidence showed that high-intensity statin is more effective when compared to medium-intensity statin at reducing non-fatal MI at up to 7 years, but the effect size is too small to be clinically important [4 studies, n=35,105].

Atorvastatin 80 mg versus atorvastatin 10 mg

- High quality evidence showed that atorvastatin 80 mg is more effective when compared to atorvastatin 10 mg at reducing non-fatal MI at up to 5 years [1 study, n=10 001], but the effect size is too small to be clinically important.

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that atorvastatin 80 mg is more effective when compared to simvastatin 20 mg at reducing non-fatal MI at up to 5 years [1 study, n=8888], but the effect size is too small to be clinically important.

Simvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that simvastatin 80 mg is more effective when compared to simvastatin 20 mg at reducing non-fatal MI at up to 7 years [2 studies, n=16,561], but the effect size is too small to be clinically important.

Stroke

Combined studies

- High quality evidence showed that there is no clinical difference between high-intensity and medium-intensity statin at reducing stroke at up to 7 years [3 studies, n=25,449].

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that there is no clinical difference between simvastatin 20 mg and atorvastatin 80 mg at reducing stroke at up to 5 years [1 study, n=8888].

Simvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that there is no clinical difference between simvastatin 20 mg and simvastatin 80 mg at reducing stroke at up to 7 years [2 studies, n=16,561].

Myalgia

Combined studies

- High quality evidence showed that medium-intensity statin is more clinically effective when compared to high-intensity statin in showing less myalgia at up to 5 years [2 studies, n=9335].

Atorvastatin 80 mg versus atorvastatin 10 mg

- Low quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg and atorvastatin 80 mg in causing myalgia events at 1 year, but the direction of the estimate of effect could favour either intervention [1 study, n=467].

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that simvastatin 20 mg is more clinically effective when compared to versus atorvastatin 80 mg in showing less myalgia events at up to 5 years [1 study, n=8888].

Rhabdomyolysis

Combined studies

- High quality evidence showed that medium-intensity statin is more clinically effective when compared to high-intensity statin in showing fewer rhabdomyolysis events at up to 7 years [5 studies, n=35,569].

Atorvastatin 80 mg versus atorvastatin 10 mg

- The difference between atorvastatin 80 mg when compared to atorvastatin 10 mg for rhabdomyolysis is uncertain as no comparative analysis could be carried out [2 studies, n=7016].

People with CKD; atorvastatin 80 mg versus atorvastatin 10 mg

- The difference between atorvastatin 80 mg when compared to atorvastatin 10 mg in people with CKD for rhabdomyolysis is uncertain as no comparative analysis could be carried out [1 study, n=3107].

Atorvastatin 80 mg versus simvastatin 20 mg

- The difference between atorvastatin 80 mg when compared to simvastatin 20 mg for rhabdomyolysis is uncertain as no comparative analysis could be carried out [1 study, n=8888].

Simvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that simvastatin 20 mg is more clinically effective when compared to simvastatin 80 mg in showing fewer rhabdomyolysis events at up to 7 years [2 studies, n=16,581].

Liver adverse events (transaminases more than 3 times the upper limit of normal)

Combined studies

- Moderate quality evidence showed that medium-intensity statin is more clinically effective when compared to high-intensity statin in showing fewer liver adverse events at up to 5 years [4 studies, n=13,211].

Atorvastatin 80 mg versus atorvastatin 10 mg

- Moderate quality evidence showed that atorvastatin 10 mg is more clinically effective when compared to atorvastatin 80 mg in showing fewer liver adverse events at up to 5 years [2 studies, n=7016].

People with CKD; atorvastatin 80 mg versus atorvastatin 10 mg

- Moderate quality evidence showed that atorvastatin 10 mg is potentially more clinically effective when compared to atorvastatin 80 mg in people with CKD in showing fewer liver adverse events at up to 5 years [1 study, n=3107].

Atorvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that simvastatin 20 mg is more clinically effective when compared to atorvastatin 80 mg in showing fewer liver adverse events at up to 5 years [1 study, n=8888].

Simvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that simvastatin 20 mg is potentially more clinically effective when compared to simvastatin 80 mg in showing fewer liver adverse events at up to 5 years [1 study, n=4200].

New-onset diabetes

Simvastatin 80 mg versus simvastatin 20 mg

- High quality evidence showed that there is no clinical difference between simvastatin 80 mg and simvastatin 20 mg in causing new-onset diabetes at up to 7 years [1 study, n=3107].

Medium intensity versus low-intensity statin

Simvastatin 20 mg versus simvastatin 10 mg

CV mortality

- Very low quality evidence suggested that there may be no clinical difference between simvastatin 20 mg and simvastatin 10 mg at reducing CV mortality at 1 year, but the direction of the estimate of effect could favour either intervention [1 study, n=197].

Non-fatal MI

- Very low quality evidence suggested that there may be no clinical difference between simvastatin 20 mg and simvastatin 10 mg at reducing non-fatal MI at 1 year, but the direction of the estimate of effect could favour either intervention [1 study, n=197].

Medium or high-intensity statin (simvastatin 20 mg or atorvastatin 80 mg) versus low-intensity statin (simvastatin 10 mg or pravastatin 40 mg)

CV mortality

- Low quality evidence suggested medium or high-intensity statin is potentially more clinically effective when compared to low-intensity statin at CV mortality at up to 2 years [3 studies, n=7249].

Non-fatal MI

- Low quality evidence suggested that there may be no clinical difference between medium or high-intensity statin when compared to low-intensity statin at reducing CV mortality at up to 2 years, but the direction of the estimate of effect favoured medium-intensity statin [2 studies, n=4351]

Low-intensity statin versus low-intensity statin

All-cause mortality

- Low quality evidence suggested that pravastatin 20 mg is potentially more clinically effective when compared to pravastatin 5 mg at reducing all-cause mortality at 4 years, but the direction of the estimate of effect could favour either intervention [1 study, n=665].

CV mortality

- Low quality evidence suggested that pravastatin 5mg is potentially more clinically effective when compared to pravastatin 20 mg at reducing CV mortality at 4 years, but the direction of the estimate of effect could favour either intervention [1 study, n=665].

Non-fatal MI

- Low quality evidence suggested that pravastatin 20 mg is potentially more clinically effective when compared to pravastatin 5 mg at reducing non-fatal MI at 4 years, but the direction of the estimate of effect could favour either intervention [1 study, n=665].

High-intensity statin versus high-intensity statin

Atorvastatin 80 mg versus rosuvastatin 40 mg

CV mortality

- Low quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg and rosuvastatin 40 mg at reducing CV mortality at 2 years, but the direction of the estimate of effect could favour either intervention [1 study, n=1385].

Non-fatal MI

- Low quality evidence suggested that there may be no clinical difference between atorvastatin 80 mg and rosuvastatin 40 mg at reducing non-fatal MI at 2 years, but the direction of the estimate of effect could favour either intervention [1 study, n=1385].

Liver adverse events (transaminases > 3 x ULN)

- Moderate quality evidence suggested that rosuvastatin 40 mg is potentially more clinically effective when compared to atorvastatin 80 mg in causing fewer liver adverse events at 2 years [1 study, n=1385].

Rhabdomyolysis

- Moderate quality evidence suggested that rosuvastatin 40 mg is potentially more clinically effective when compared to atorvastatin 80 mg in showing fewer rhabdomyolysis events at 2 years [1 study, n=1385].
- The difference between atorvastatin 80 mg when compared to rosuvastatin 40 mg in people with CKD for rhabdomyolysis events is uncertain as no comparative analysis could be carried out [1 study, n=34].

11.7.2 Economic

Published literature

- One cost–utility analysis found that statins (as a combined single class) were cost effective compared to no treatment for the **primary prevention** of CVD in men aged 65 at **1.5% annual risk of CHD** (ICER: £11,200 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that 5-year treatment with low-intensity statins was dominant (less costly and more effective) compared to no treatment over a 15-year period for the **primary**

prevention of CVD in men aged 45–64. This analysis was assessed as directly applicable with minor limitations.

- One cost–utility analysis found that high-intensity statins were cost effective compared to no treatment for the **primary prevention** of CVD in **people with LDL cholesterol <3.36 mmol/litre and high-sensitivity C-reactive protein >2.0 mg/litre** (ICER: £16,465 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that statins (as a combined single class) were cost effective compared to no treatment for the **secondary prevention** of CVD in men aged 65 (ICER: £9100 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that high-intensity statins were cost effective compared to medium- or low-intensity statins for the **secondary prevention** of CVD in adults aged 65 with **acute coronary syndrome** (ICER: £4397 per QALY gained), but were not cost effective for those with **coronary heart disease** only (ICER: £28,361 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.
- One cost–utility analysis found that high-intensity statins were cost effective compared to medium-intensity statins for the **secondary prevention** of CVD in adults aged 60 (ICER: £5319 per QALY gained for simvastatin 80 mg; £3172 per QALY gained for atorvastatin 80 mg; £12,484 for rosuvastatin 40 mg). This analysis was assessed as directly applicable with potentially serious limitations.
- One cost–utility analysis found that statins were cost effective compared to placebo for the prevention of CVD in **men aged 65 with CKD** (ICER: £11,730 per QALY gained) but were not cost effective for **women aged 65 with CKD** (ICER: £21,760 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

New cost-effectiveness analysis

- 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.

11.8 Recommendations and link to evidence

11.8.1 Statins for the prevention of CVD

Recommendations in this section update and replace those in Statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94)].

Recommendations	**46. Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. [2008]** **47. When a decision is made to prescribe a statin use a statin of high intensity[4] and low acquisition cost. [new 2014]** **48. The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. [new 2014]** **49. Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia. Include all of the following in the assessment:** • **smoking status** • **alcohol consumption** • **blood pressure (see Hypertension [NICE clinical guideline 127])** • **body mass index or other measure of obesity (see Obesity [NICE clinical guideline 43])** • **total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides** • **HbA_{1c}** • **renal function and eGFR** • **transaminase level (alanine aminotransferase or aspartate aminotransferase)** • **thyroid-stimulating hormone. [new 2014]** **Primary prevention** **50. Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. [new 2014]**

[4] See Table 36 for statin classification.

51. Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes. (See Behaviour change: individual approaches [NICE public health guidance 49].) [new 2014]

52. Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. [new 2014]

53. If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. [new 2014]

54. Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]

55. For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48). [new 2014]

Secondary prevention

56. Start statin treatment in people with CVD with atorvastatin 80 mg[5]. Use a lower dose of atorvastatin if any of the following apply:

- **potential drug interactions**
- **high risk of adverse effects**
- **patient preference. [new 2014]**

57. Do not delay statin treatment in secondary prevention to manage modifiable risk factors. [2014]

58. 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]

People with Type 1 diabetes [Recommendations in this section [59-61] update and replace recommendations 1.10.1.3, 1.10.1.4, 1.10.1.5 and 1.10.2.4 from Type 1 diabetes (NICE clinical guideline 15)]

59. Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. [new 2014]

[5] At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

	60. Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who: • **are older than 40 years or** • **have had diabetes for more than 10 years or** • **have established nephropathy or** • **have other CVD risk factors. [new 2014]** **61. Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]** **People with Type 2 diabetes** **62. Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014] [This recommendation updates and replaces recommendations 1.10.1.2, 1.10.1.3, and 1.10.1.5 from Type 2 diabetes (NICE clinical guideline 87).]** **People with CKD** **63. Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[6].** • **Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 64) and eGFR is 30 ml/min/1.73 m^2 or more.** • **Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. [new 2014]**
Relative values of different outcomes	All-cause mortality, CV mortality, non-fatal MI, stroke and quality of life were considered critical outcomes. Myalgia, new-onset diabetes, liver adverse events and rhabdomyolysis were considered relevant outcomes. LDL-cholesterol reduction was included in the review protocol to ensure information would be available if the GDG needed to make recommendation about individual drugs and about targets. The GDG did not consider that the use of a surrogate outcome – evidence of LDL-cholesterol lowering – was sufficient to make a recommendation for statin treatment.
Trade-off between clinical benefits and harms	High- and medium-intensity statin intensity groups had a beneficial effect on non-fatal MI. There was small evidence of benefit for low intensity statins although the effect may not be clinically important. The difference between high-intensity statins and medium-intensity statins for non-fatal MI was small and may not be clinically important. The subgroup analysis according to population showed evidence of benefit for non-fatal MI in people with and without CVD, and small benefit for people with type 2 diabetes and CKD, which may not be clinically important. There was a small benefit on CV mortality for all intensity statins but this may not be clinically important. Evidence for stroke was inconsistent with statin intensity, and only

[6] See the forthcoming updated guideline on chronic kidney disease for CKD classification (publication expected 23 July 2014). People on renal replacement therapy are outside the scope of this guideline.

	a small benefit was found for stroke with medium-intensity statin. There was a small benefit for all-cause mortality which may not be clinically important. Overall there was no consistent trend for the rates of adverse events and intensity of statin. There was no increase in myalgia with statin intensity. Elevated transaminases, rhabdomyolysis events and increased rates of new-onset diabetes were seen in most intensity groups but there was no clear gradation across them and the effect sizes were small. However there was a consistent higher rate of adverse events for simvastatin 80 mg compared with other higher intensity statins. The pooled estimates of LDL-cholesterol lowering correlated with statin intensity. Clinical event rates and LDL-cholesterol reduction did not appear to be dependent upon study follow-up. No evidence was found that specifically examined the use of statins people aged over 75 years, and many studies excluded this population. No evidence was found for the outcome of quality of life. The GDG noted that the evaluation of individual outcomes may underestimate the total clinical benefit of statins. We did not examine composite outcomes (for example reduction in all CV events) because of the inconsistent reporting of combined outcomes in the RCT evidence. Individual patient-level data were not available. When making recommendations the GDG considered the findings of a systematic review[258] reporting on NNT for composite outcomes (see Section 11.5).
Economic considerations	One hundred and twenty-nine published economic articles were identified that evaluated the cost effectiveness of statins for one or more of the population groups of interest in this chapter. Almost all of these had very low applicability to this guideline, as they were carried out several years ago or in other countries and so the costs used, most critically the costs used for statins, were out of date. Consequently their conclusions were not applicable to a current UK context and so they were excluded. The 6 most applicable studies were reviewed for this guideline. **Secondary prevention** Three published studies were included which looked at the use of statins for secondary prevention of CVD. Ward 2005[269] is the economic study carried out to inform NICE technology appraisal 94,[182] which this guideline updates. It found that statins (meta-analysed as a single class) were cost effective compared to placebo for secondary prevention. In its base case analysis it looked only at the effects of statins on CHD events, however in additional scenarios (which the NICE technology appraisal decided were the most relevant analyses) it also looked at the effects of statins on a broader definition of CVD, including strokes. In this analysis the ICERs were below £14,000 per QALY gained for both men and women at all ages modelled (45, 55, 65, 75, 85). This study did however use discount rates of 6.0% for costs and 1.5% for benefits. A sensitivity analysis on the base case results showed that ICERs would be increased if discount rates of 3.5% had been used. However, this model also used costs of statins (weighted average of £317 per year) much higher than current UK costs. If current costs had been used the ICERs would have been lower. It is not possible to be entirely sure how far these 2 effects would cancel each other out. NCCPC 2008[176] is the second of 3 economic models conducted for NICE clinical guideline 67, which this guideline also updates. It compared high-intensity statins (atorvastatin 80 mg or simvastatin 80 mg) with lower-intensity statins (a mixture of medium-intensity and low-intensity statins using the classification in this guideline). It found that atorvastatin 80 mg was cost effective for patients with ACS (ICER: £4397 per QALY gained), but not for patients with CHD but no ACS (ICER: £28,361 per QALY gained). However, when the (then high) cost of atorvastatin 80 mg (£368 per year) was replaced with the lower cost of simvastatin 80 mg (£65 per year), assuming equal efficacy between them, high-intensity statins became dominant (more effective and less costly) compared to lower-intensity statins. The current UK cost of atorvastatin 80 mg is £35 per year.

Ara 2009[21] is a systematic review and economic evaluation carried out for the UK Health Technology Assessment programme. It compared 3 different high-intensity statins against medium-intensity statins (simvastatin 40 mg) for people with recent ACS. It found that all 3 high-intensity statins were cost effective compared to medium-intensity statins at a cost effectiveness threshold of £20,000 per QALY gained. When a projected possible future cost of atorvastatin 80 mg (£92 per year) was used, atorvastatin 80 mg was the preferred treatment since it was dominant compared to simvastatin 80 mg, and the ICER for rosuvastatin 40 mg compared to atorvastatin 80 mg was above £30,000 per QALY gained.

The original cost–utility analysis carried out for this guideline found 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 to no treatment for people who already have CVD (ICER: £2959 per QALY gained for atorvastatin 20 mg compared to no treatment; £3410 per QALY gained for atorvastatin 80 mg compared to no treatment). These results were robust to the sensitivity analyses conducted and for all subgroups by age and sex.

This 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 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% more effective in relative terms at decreasing CV events and there was no loss in utility due to greater 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 in decreasing CV events and there was no loss in utility due to greater adverse events. Clinical trials have compared atorvastatin 80 mg with medium-intensity statins (atorvastatin 10 mg, simvastatin 20 mg) but no trials in our clinical review have compared atorvastatin 80 mg with atorvastatin 20 mg or 40 mg.

The GDG concluded that high-intensity statins are the most clinically effective option for secondary prevention of CVD and are cost effective compared to all other options, and so should be recommended.

Primary prevention

Three published studies were included which looked at the use of statins for primary prevention of CVD.

Ward 2005[269] looked at primary prevention in addition to secondary prevention. It stratified the primary prevention population in terms of annual risk of CHD events, although these were also converted into the equivalent risks of CVD events. In this analysis it found that statins (as a single class) were cost effective at a threshold of £20,000 per QALY for men aged 65 or under at all annual CVD risks investigated from 1.1% (that is a 10-year risk of 10%) upwards, for men aged 75 from 2.4% (22%) and for men aged 85 from 3.7% (31%). For women aged 65 or under it was again cost effective to use statins at all risk levels evaluation from 1.1% (10%) upwards, for women aged 75 from 1.8% (17%) and for women aged 85 from 2.5% (22%). However, as discussed above, the applicability of this study to the current context is impaired due to the fact that statin costs have since reduced, and the standard discount rates used in NICE evaluations have changed, and so if this study were repeated the risk thresholds at which treatment is cost effective would be expected to change.

McConnachie 2014[163] is a follow-up study which investigated the hospital admissions and resource use of the men (aged 45–64 at the start) recruited to the WOSCOPS trial of pravastatin 40 mg in Scotland. The trial lasted an average of 4.9 years, after which randomisation ended; 5 years later the proportions of participants in the control and intervention arms taking any statin or other lipid-lowering treatment were similar

(35.2% compared to 38.7%). This study looked at healthcare expenditure on the participants during the trial and the 10 following years, using linked medical records. It found that 5 years of low-intensity statin treatment was dominant (less costly and more effective) compared to no treatment. Its calculations were based on 2012 UK hospital costs and an annual cost of statins of £36, and it is therefore highly applicable to the current UK context.

Choudhry 2011[49] is an economic model based on the JUPITER study of rosuvastatin 20 mg compared with placebo in a group of participants with relatively low LDL cholesterol (below 3.36 mmol/litre). Participants were given statins if their high-sensitivity C-reactive protein (hs-CRP) level was greater than 2.0 mg/litre, rather than the decision being based on a measure of CV risk. The study found that high-intensity statins were cost effective for such people (ICER: £16,465 per QALY gained), but with a large margin of uncertainty: the probabilistic ICER results were £18,018 (95% CI: £6796 to £41,024) per QALY gained. Sensitivity analyses showed that the ICER would be above £20,000 if the effectiveness of statins was reduced, adverse events were higher, or the duration of treatment effect was reduced to 15 years, as well as for those with low CV risk (as measured by the Framingham risk calculator). The model used US costs for rosuvastatin (higher than current UK costs) for the first 7 years, but then assumed that the cost would decrease in future (to below current UK costs) after rosuvastatin comes off patent. It also did not compare the cost effectiveness of rosuvastatin to that of less costly high-intensity statins. For these reasons it is unclear if the conclusions of this study would be applicable to the current UK context, where the decision to initiate statin treatment is based on CV risk level, and the GDG does not recommend routine screening by hs-CRP levels.

The original economic analysis found that high-intensity statin treatment using atorvastatin 20 mg is cost effective compared to medium-intensity statin treatment for people 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 who have a QRISK2 score above 8.7%. Medium-intensity treatment is cost effective compared to no treatment or low-intensity treatment at all realistic risk levels. At a QRISK2 risk score of 10% the ICERs compared to no treatment were £4125 per QALY gained for atorvastatin 20 mg and £4875 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 to all sensitivity analyses, except for when the risk ratios for the effectiveness of statin treatment were all increased (that is, the benefits of treatment were decreased) to the upper confidence interval of the risk ratios for all CV events or when the risk ratio for non-CV mortality was assumed to be worse for high-intensity statins that for medium-intensity statins.

The base case analysis did not include the potential effects of adverse events other than new-onset diabetes. Two scenario analyses were 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 in that situation.

The GDG concluded that high-intensity statins are the most clinically effective option for primary prevention of CVD and are cost effective compared to all other options and so should be recommended.

Type 2 diabetes

No published cost-effectiveness evidence was found relating to people with type 2 diabetes.

The original economic analysis explored the cost effectiveness of statin treatment for primary prevention in people with type 2 diabetes using the UKPDS risk tool. The results are summarised in Section 11.6.2.3 above. However the GDG chose not to recommend the UKPDS tool for risk assessment, and so those findings are not directly relevant to the GDG's conclusions. Instead, risk in people with type 2 diabetes should

	be assessed using the QRISK2 risk tool. Therefore the results reported above for primary prevention apply equally to people with type 2 diabetes at the same CV risk levels as those without diabetes. The GDG therefore concluded that high-intensity statins are the most clinically effective option for prevention of CVD in people with type 2 diabetes and are cost effective compared to all other options and so should be recommended. **Type 1 diabetes** No published cost-effectiveness evidence was found relating to people with type 1 diabetes. People with type 1 diabetes were not explored as a separate subgroup in the original economic analysis as the clinical review found no evidence to justify assuming a different effectiveness for statin therapy in people with type 1 diabetes compared to other populations, and because no alternative risk tool was recommended that is specific to people with type 1 diabetes. **Chronic kidney disease** One study (Erickson 2013[86]) was reviewed focussing on people with CKD. This was based on the effectiveness of all statins, assessed as a single class, versus placebo as assessed in a Cochrane meta-analysis[193] and US costs. This found that statins were cost effective compared to placebo in the base case for men aged 65 (ICER: £11,730) but not for women (ICER: £21,760) and not under all sensitivity analyses. Statins were more cost effective for older people, people at earlier stages of CKD, and people at higher risk of CVD. The study did not assess the cost effectiveness of different intensities of statin compared with each other. Due to differences in US and UK costs, this is not fully applicable to a current UK context. People with CKD were not explored as a separate subgroup in the original economic analysis conducted for this guideline, as the clinical review found no evidence to justify assuming a different effectiveness for statin therapy in people with CKD compared to other populations, and because no alternative risk tool was recommended that is specific to people with CKD.
Quality of evidence	The majority of the evidence for all-cause mortality and CV outcomes was of high or moderate quality. Evidence for myalgia varied from high to low quality. The majority of evidence for adverse liver events was of high or moderate quality. Evidence for new-onset diabetes was of high or moderate quality. The studies were underpowered for the rare adverse event outcome of rhabdomyolysis and the quality of evidence for this outcome varied from high to very low. There was no evidence of heterogeneity between either the type 2 diabetes or CKD populations and the other populations with respect to the majority of outcomes. Evidence at the study level showed LDL-cholesterol reduction correlated with intensity. However, the subgroup analysis demonstrated heterogeneity in each intensity group. There was some indication that the final statin LDL-cholesterol reduction may be linked to baseline LDL cholesterol, and this could explain the heterogeneity.
Other considerations	**Secondary prevention** In CG67 high-intensity statin treatment was recommended for secondary prevention of CVD. Atorvastatin 80 mg or simvastatin 80 mg was recommended for people with ACS. For the remaining secondary prevention population treatment was recommended with simvastatin 80 mg if people did not achieve a reduction in total and LDL cholesterol on simvastatin 40 mg. In the clinical and cost-effectiveness analysis for this update high-intensity statins as a group are a cost-effective treatment for all secondary prevention populations. Since atorvastatin 80 mg was previously recommended for people with ACS, the GDG discussed the appropriate choice of atorvastatin for non-ACS secondary prevention population. The GDG judged that it is very likely that increasing doses of atorvastatin have increasing efficacy. The GDG believed the additional reduction in CV events caused by atorvastatin 80 mg compared to 20 mg is unlikely to be as large as the

additional reduction in LDL cholesterol.[255] However it is very likely to be large enough (2% additional relative reduction in CV events) to cause atorvastatin 80 mg to be cost effective compared with atorvastatin 20 mg at a threshold of £20,000 per QALY. The GDG consequently recommends that statin therapy for secondary prevention should normally be initiated with atorvastatin 80 mg. The GDG considered that higher doses of atorvastatin may lead to an increase in adverse events. GDG members' experience however was that when atorvastatin 80 mg is used for people with ACS it is generally well tolerated. At the relatively low levels of adverse events seen in the trial evidence, atorvastatin 80 mg would be likely to remain cost effective even given an increase in these adverse events. Most adverse events are temporary and reversible. Hence the GDG recommends routine testing of individuals receiving statin treatment and recommends that those experiencing an adverse event which may be connected to their treatment should decrease the dose or intensity of statin which they are receiving (see the following section of this chapter). This will end the adverse effects in most cases if the event was caused by the statin.

Simvastatin 80 mg is more expensive than any dose of atorvastatin, and there is no evidence for its superiority to atorvastatin 20 mg or 40 mg in reducing CV events. A meta-analysis[141] found simvastatin 80 mg to have a lesser effect in reducing LDL cholesterol compared with atorvastatin 20 mg, 40 mg or 80 mg. The MHRA has advised: "There is an increased risk of myopathy associated with high-dose (80 mg) simvastatin."[13] Since equivalent or greater benefits can be obtained from atorvastatin, with a lower risk of myopathy, the GDG judged that there is no reason for considering simvastatin 80 mg for any people newly initiating treatment for secondary prevention. Patients who have already been taking simvastatin 80 mg for a period of time and have had no adverse reactions to it may continue to take it if that is preferred to switching to atorvastatin 80 mg.

One study (SATURN 2011[194]) has compared atorvastatin 80 mg with rosuvastatin 40 mg for secondary prevention. The clinical outcomes of this study were inconclusive. No other studies have compared the effectiveness of atorvastatin with rosuvastatin for reducing CV events, whilst meta-analysis indicates that the effectiveness of atorvastatin 80 mg and rosuvastatin 40 mg in reducing LDL cholesterol are similar.[141] The GDG were hence unable to judge if rosuvastatin 10 mg, 20 mg or 40 mg would be more effective than atorvastatin 80 mg in reducing CV events. Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost effective. In the absence of trial evidence of greater effectiveness the GDG are therefore unable to recommend the use of rosuvastatin.

Primary prevention

The health economic modelling indicated that it is cost effective to treat people with atorvastatin 20 mg, 40 mg or 80 mg at QRISK2 risks below 10%. In considering the risk threshold above which statins should be offered, the GDG took account of the uncertainty regarding the frequency of adverse events in routine clinical practice, which may be higher than in clinical trials, the uncertainty around the magnitude of the effectiveness of statins, and the accuracy of the QRISK2 tool itself, as well as the cost-effectiveness base case results and sensitivity analyses. The GDG concluded that the appropriate level of risk above which high-intensity statin treatment should be initiated was 10% as measured using QRISK2. For those at 10% risk of future CV events, atorvastatin 20 mg is likely to decrease this risk by a large proportion, and higher doses of atorvastatin would be likely to decrease it by only a modest extra amount. Consequently the GDG judged that it would be prudent to recommend atorvastatin 20 mg as the preferred initial treatment for primary prevention. People at higher baseline risk, or those with additional factors such as treatment for antipsychotic disorders are likely to benefit from higher doses of atorvastatin. The GDG therefore considered it appropriate in the monitoring recommendations (see Section 11.8.2) to suggest increasing atorvastatin dose in these people. The GDG considered that

individuals with lower risk may have greater potential to reduce their risk to a safer level by altering lifestyle factors, whereas those at high risk would be likely to retain a substantial risk even after all lifestyle factors were optimised.

Given the cost effectiveness of high-intensity statin treatment at relatively low risk thresholds, the GDG discussed whether it was appropriate to recommend that statins be offered on an age-alone basis – that is, to all people above a certain age, rather than according to CV risk. The GDG was reluctant to do this as an age limit would be somewhat arbitrary and the GDG wished to emphasise the potential reduction of premature morbidity and mortality that would also accrue to younger people with other CV risk factors when appropriately assessed and treated.

The GDG was aware that a recommendation for treatment with atorvastatin 20 mg, with a possibility to increase further in some people, represents a change in current practice and will result in an increased proportion of the population being offered treatment. The GDG recognised the importance of the principles outlined in the NICE Medicines adherence guideline[188] and the importance of informed choice in the decision to take any drug. This is particularly important in primary prevention for people at lower risk.

The GDG added recommendations to ensure that lifestyle modification is offered and where possible facilitated by healthcare professionals and that people are given an opportunity to review their risk level if they have attempted lifestyle modification. The JBS3 lifetime risk tool provides useful ways of presenting information about effects of lifestyle and other modifications.

While a 10% threshold on QRISK2 results in statins being offered to people at a lower risk than previously, the GDG recognised that there are people whose risk is above 20% who remain untreated. For people at higher levels of risk delaying the offer of statins until lifestyle modification is achieved may not be appropriate.

Primary prevention in people with type 2 diabetes

The GDG discussed the expectation that people with type 2 diabetes are likely to have a high risk of CVD, similar to that of the general secondary prevention population. This concept was included in previous guidelines and considered robust based on epidemiological evidence. People with type 2 diabetes without CVD have been recruited into secondary prevention studies on the basis of being regarded as having an equivalent risk. Most people with type 2 diabetes are at higher risk of CVD than those without diabetes due to risk factors such as raised lipid levels, raised blood pressure, and higher BMI. These risks will rise further over time, and hence the GDG judged that the sooner statin treatment can be initiated, the more beneficial it will be. Atorvastatin 80 mg is cost effective at QRISK2 risk thresholds below 10%. In considering the risk threshold above which statins should be offered, the GDG took account of the uncertainty regarding the frequency of adverse events in routine clinical practice, which may be higher than in clinical trials, the uncertainty around the magnitude of the effectiveness of statins, and the accuracy of the QRISK2 tool itself, as well as the base case cost-effectiveness results and sensitivity analyses. The GDG agreed to treat at a threshold of 10% risk over 10 years and to recommend that treatment is started with atorvastatin 20 mg.

Primary prevention in people with type 1 diabetes

The GDG used their professional judgement and knowledge from epidemiological studies to decide on appropriate drug recommendation for people with type 1 diabetes. There is no appropriate risk tool to use in people with type 1 diabetes. The GDG considered that CVD risk in type 1 diabetes is greater than that in people without diabetes.

Lifestyle factors, especially the increasing incidence of obesity and the metabolic syndrome in type 1 diabetes, increase that risk. High-intensity statins are cost effective in primary prevention at relatively low risk levels in people without type 1 diabetes and people with type 1 diabetes are likely to benefit at least as much as the low-risk primary

prevention population. The GDG acknowledged that specialists consider they can identify those patients with type 1 diabetes who are most at risk of developing CVD and that this is associated with length of time the person has diabetes for, their age and evidence of nephropathy. Type 1 diabetes is often diagnosed in childhood and by the time people become adults they will have had diabetes for up to 10 years. The GDG agreed using informal consensus that all adults with type 1 diabetes may benefit from treatment with a statin and that statin treatment should be considered. They agreed that statin treatment should be offered to adults with any additional risk factors to their type 1 diabetes and made a recommendation listing common factors such as age over 40 years, length of time people have had diabetes for, presence of additional CVD risk factors and evidence of abnormal renal function. People with Type 1 diabetes without evidence of CVD should start statin treatment on atorvastatin 20 mg.

Primary and secondary prevention in people with chronic kidney disease

The GDG used information from the evidence review, epidemiological data, the advice of a co-opted renal physician with a specialist interest in CVD prevention, and the need to provide practical recommendations for people with CKD to inform its decisions about recommendations for people with CKD. Different stages of CKD are differentiated using cut-off points and the GDG recognised that people may have results on these boundary levels. There is concern that people with more severe CKD are at greater risk of adverse events as a result of taking high doses of statins than people without CKD, and there are some restrictions in SPCs for this population. For these reasons the GDG agreed that all people with CKD should start treatment on atorvastatin 20 mg rather than a higher dose. In people with eGFR greater than 30ml/min/1.73m^2 the dose can be increased up to atorvastatin 80 mg if tolerated so that people may gain the maximum possible benefit.

For people with eGFR below 30ml/min/1.73m^2 there are increased concerns about use of medications as renal function deteriorates. Cardiac mortality is also more associated with arrhythmias than atherosclerosis in this population. The GDG considered that caution was required in this group. A higher dose of atorvastatin than 20 mg should not be given without discussion with the patient's renal team.

The GDG acknowledged that the evidence base for the use of statins in people with CKD stages 3b to 5 is the SHARP trial which studied a combination of simvastatin 20 mg with ezetimibe versus placebo. The consensus, informed by the expert, was that there was no evidence of excess risk with atorvastatin compared to simvastatin and there was no contraindication to using atorvastatin 20 mg as an initial drug.

People requiring renal replacement treatment are outside the scope of this guideline.

For all situations where the recommendations are to start treatment at 80 mg of atorvastatin it may be appropriate to start treatment at a lower dose if there is concern about drug interactions or potential side effects.

Older people

The GDG noted that the majority of trials excluded people aged over 75 years. Only 2 studies were identified specifically in adults older than 65 years,[69,235,236] and people aged over 85 years were excluded. The GDG were aware that people aged 85 years and older have a greater absolute risk of CV events compared with younger people, and therefore might have a greater likelihood of clinical benefit with statins. The GDG also acknowledged that older people are more likely to have other comorbidities, poorer renal function, shorter life expectancy and to be taking other medication. The GDG made a recommendation that statin treatment should be considered in people over 85 years but added detail to make it explicit that the benefit may only be in reduced non-fatal MI. Consideration of risk and benefits and factors such as polypharmacy, comorbidity, frailty and life expectancy are particularly important in older age groups.

Advice to people on low- and medium-intensity statins

Following CG67 many people are taking simvastatin 40 mg or equivalent for prevention

of CV events. The change to cost effectiveness means that higher-intensity statins at higher doses can now be prescribed. The GDG recognised that many people are stable on an existing treatment and considered that it was a matter for discussion between patients and their doctors as to whether to change dose. People will be getting benefit from lower-intensity statins and they can be reassured about this.

Assessment prior to statin treatment

The GDG updated the recommendation from the previous guideline to use HbA_{1c} for assessment of pre-diabetes and diabetes and for the use of non-HDL cholesterol. The World Health Organisation in 2011 concluded that HbA_{1c} can be used as a diagnostic test for diabetes. An HbA_{1c} of 48 mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes and HbA_{1c} of 6.0–6.4% indicates high risk of diabetes and lifestyle advice is recommended.

Discussion of grouping of statins according to LDL-cholesterol reduction

The GDG was aware that the methodology involved in the grouping of statins into low-, medium- and high-intensity groups can be criticised as arbitrary. It is however a grouping recognised in clinical care and is based an analysis by Law 2003.[141] A more recent analysis of 75 head-to-head statin trials (minimum duration 4 weeks)[274] provided similar results as the subgroup analysis for LDL-cholesterol outcomes according to statin intensity included in this guideline.

The analysis by Law 2003 is a meta-analysis of 164 short term trials of statins versus placebo that determined the efficacy of statins in reducing total cholesterol and LDL cholesterol. The analysis included RCTs of 2 weeks minimum duration and with fixed statin dose throughout the RCTs. The absolute and percentage reductions in LDL cholesterol were reported. More recent systematic reviews have included fewer studies. For example CTT 2010[12] included 26 RCTs because their inclusion criteria were RCTs with more than 1000 participants and study duration of more than 2 years. The studies we included in this guideline when determining the efficacy of statins in reducing all-cause mortality, CV events and adverse events included those with a follow up of 1 year or more, with no limit on number of participants. The 1 year minimum follow-up was chosen as many studies of less than a year do not report all-cause mortality, CV and adverse event data. In total we included 46 RCTs. Tests for subgroup differences in the statin versus placebo RCTs showed that heterogeneity in our meta-analyses could be explained by grouping the statins according to Law 2003. The findings for reduction of all-cause mortality and CV outcomes were consistent with the GDG's decision on statin intensity grouping according to absolute LDL-cholesterol reduction.

The GDG discussed the potential use of individual patient-level data (IPD) to inform the use of statins. The efficacy of statins and LDL-cholesterol reduction has been examined in a number of reports by the CTT using IPD.[12,26,169] The GDG noted that other meta-analyses had derived different relationships linking changes in LDL cholesterol with CVD outcomes.[255] The use of IPD could explore whether risk reduction varies with baseline risk as has been suggested in published studies and how treatment with statins impacts on risk as assessed by validated risk assessment tools. The GDG made a research recommendation for this.

11.8.2 Follow-up of people started on statin treatment and intolerance of statin

Recommendations	**64. Measure total cholesterol, HDL cholesterol and non HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non HDL cholesterol. If a greater than 40% reduction in non HDL cholesterol is not achieved:** **• discuss adherence and timing of dose** **• optimise adherence to diet and lifestyle measures** **• consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014] [This recommendation updates and replaces recommendation 1.10.2.7 from Type 1 diabetes (NICE clinical guideline 15).]** **65. If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. [new 2014]** **66. Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:** **• stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin** **• reducing the dose within the same intensity group** **• changing the statin to a lower intensity group. [new 2014]** **67. Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral. [new 2014]** **68. Provide annual medication reviews for people taking statins.** **• Use these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors.** **• Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. [new 2014]** **69. Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. [new 2014]**
Relative values of different outcomes	These recommendations were informed by the evidence review of statin efficacy, the evidence review on prediction of adverse effects of statins and the evidence review on interventions to increase adherence to statins. Changes in lipid

	subfractions in trials after starting statin therapy also informed these recommendations.
Trade-off between clinical benefits and harms	The evidence review and health economic modelling found that statin treatment is of benefit to people at risk of CVD. People however often find it difficult to take drugs and suffer side effects from them. Supporting people in getting as much benefit as possible from statins while reducing side effects would be of benefit to patients.
Economic considerations	The original economic analysis conducted for this guideline found that all intensities of statin treatment were cost saving or cost effective compared to no treatment for those at moderate and high risk of CVD when statins of low acquisition cost are used. Therefore, if someone is not able to take the highest intensity statin recommended it will still be cost effective for them to take the most clinically effective dose of a statin which they can tolerate, with the exception of rosuvastatin which is much more costly than the other available statins and so would not be cost effective.
Quality of evidence	Evidence from the statin efficacy review varied from high to very low quality for the adverse event outcomes. Evidence from the review of interventions to improve adherence was of low or very low quality. Evidence from the review on predictors of adverse events in patients on statin therapy was of moderate or low quality.
Other considerations	The clinical management of people taking statins was informed by the evidence reviews and by the clinical experience of the GDG. The health economic modelling found that it is cost effective to give people high dose atorvastatin. The GDG did not therefore set a target for treatment as people taking atorvastatin 80 mg are on the highest available dose. The GDG recommended that some groups of people are started on atorvastatin 20 mg. The GDG considered that a cholesterol measurement should be taken at 3 months. Ideally one would wish to see a reduction in cholesterol of 40% but there are wide confidence intervals around the estimated LDL-cholesterol level reduction achieved by individual drugs. If this reduction is not achieved or the person is clinically judged to be at higher CV risk than that predicted by QRISK2 the GDG recommended that people on lower doses of atorvastatin could be offered a higher dose. If people are already on a higher dose the review is an opportunity to discuss adherence and to emphasise other aspects of CV risk reduction. The GDG discussed the management of patients with side effects taking statins. The GDG recognised that people report side effects with statins and are often reluctant to continue the statin. The GDG considered that in general statins have low rate of side effects and adverse events such as muscle pain reported by patients taking statins may have different causes. The GDG considered that true statin intolerance is not common and a number of strategies are available when people report side effects. The GDG decided that patients should be re-challenged with a statin given the non-specific nature of many statin-associated side effects. If the original statin was not tolerated another statin of similar intensity should be tried before resorting to a lower intensity group.[130,150]The GDG agreed that patients should take the highest tolerated dose of statin therapy as higher intensity statins are more efficacious in reducing CV events. The GDG noted there was outcome evidence for pravastatin at low doses – mostly 10 mg. Patients should be on a statin even at low dose in preference to any other lipid-lowering drug and patients should be informed that they will benefit even at lower doses and intensities. The GDG decided that statin intolerance should be defined clinically as the inability to tolerate 3 different statins. The evidence reviews for this guideline did not find clear benefit for other drugs so the GDG were not able to recommend alternatives to statins. In patients at high risk of CVD, for example people who have already had a CV event, and who are intolerant of statins advice should be sought from a specialist about other possible treatment options. The GDG recognised that there might not be a suitable drug intervention available for some people at risk and that this should be

	acknowledged. Section 11.11 discusses the initial advice and monitoring for adverse events appropriate when people are initiated on statin treatment. Once a person is stable on their tolerated dose of statin annual review is recommended. This is an opportunity to review adherence and re-inforce lifestyle modification. A measurement of non-HDL cholesterol may be useful to inform the discussion but the guideline as the guideline is not recommending a target cholesterol level, repeated measurements more regularly than this are not recommended.

11.8.3 Lipid measurement and referral

Recommendations	**[Recommendations in this section [70 to 78] update and replace recommendation 1.9.4 from Type 2 diabetes (NICE clinical guideline 87)]** **70. Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. [2008]** **71. Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. [new 2014]** **72. Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. [new 2014]** **73. Exclude possible common secondary causes of dyslipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. [new 2014]** **74. Consider the possibility of familial hypercholesterolaemia and investigate as described in Familial hypercholesterolaemia (NICE clinical guideline 71) if they have:** • **a total cholesterol concentration more than 7.5 mmol/litre and** • **a family history of premature coronary heart disease. [new 2014]** **75. Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease. [new 2014]** **76. Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control. [new 2014]** **77. In people with a triglyceride concentration between 10 and 20 mmol/litre:** • **repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and** • **review for potential secondary causes of hyperlipidaemia and** • **seek specialist advice if the triglyceride concentration remains above 10 mmol/litre. [new 2014]** **78. In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre:** • **be aware that the CVD risk may be underestimated by risk assessment**

	tools and • **optimise the management of other CVD risk factors present and** • **seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. [new 2014]**
Relative values of different outcomes	The GDG were interested in measurements which are used in validated assessment tools, practical use and accuracy of measurement.
Trade-off between clinical benefits and harms	Identification of people most likely to suffer from CVD events would help target monitoring and reduce adverse events. Identification of people most likely to have hyperlipidaemias requiring additional specialist management will benefit patients. While blood tests may not be a significant harm they can cause discomfort to patients and reducing the monitoring required for those at least risk would benefit patients and reduce costs to the NHS.
Economic considerations	Assessment of a patient by a specialist is more expensive than assessment by a GP. GPs should seek to eliminate any alternative causes of dyslipidaemia before seeking specialist assessment.
Quality of evidence	Specific reviews were not conducted to inform these recommendations. They were based on the other evidence reviews and GDG consensus.
Other considerations	The GDG reviewed the use of lipid subfractions in risk calculation tools. While Framingham used fasting lipid samples at each visit, QRISK2 is based on primary care records and much of the data is likely to be non-fasting. Both risk tools use total and HDL cholesterol in their calculation and the recommendation to use these is therefore unchanged from CG67. The GDG used their knowledge and experience to inform recommendations about elements of full lipid profile and of criteria for referral. Formal review of the evidence was not conducted. The recommendations were reached by informal consensus. The measurement of cholesterol, cholesterol sub-fractions and triglycerides are necessary to ensure treatment is appropriate. The GDG discussed that the Friedewald equation for calculation of LDL-cholesterol as commonly used for risk assessment requires a fasting sample and triglycerides below 4.5 mmol/litre. It is derived from a small number of patients (130) and the original study included very few patients with diabetes (<30). The GDG were aware that a recent very large database analysis had revealed excess variance and bias in the calculation of LDL cholesterol such that a complicated table of correction factors would have to be applied by clinical laboratories.[160] The formula was also limited in its utility at low LDL-cholesterol levels as seen with high-intensity statin treatment.[159] The use of direct LDL-cholesterol measurement is limited by cost and availability in the NHS. Meta-analyses of CVD outcomes in relation to lipid fractions by the Emerging Risk Factors collaboration and others have consistently shown the superior predictive value of non-HDL cholesterol (that is, the difference between total and HDL cholesterol) on CV events.[73] Non-HDL cholesterol does not require a fasting blood sample. The GDG decided that the use of non-HDL cholesterol was preferable to calculated or measured LDL cholesterol given its greater practicality The GDG considered the role of secondary causes of hyperlipidaemia. Epidemiological data shows a high prevalence of excess alcohol intake and an increasing population burden of obesity due to excess calorie intake. The allied complications of obesity are type 2 diabetes and non-alcoholic fatty liver disease. These environmental factors raise total cholesterol and triglyceride levels and can be managed by lifestyle measures. Poor glycaemic control in diabetes affects cholesterol and triglyceride metabolism as much as glucose. Achievement of good glycaemic control will result in a more accurate estimate of lipid levels. Hypothyroidism results in hypercholesterolaemia and is associated with excess CVD risk. The GDG noted that statin toxicity is magnified in

patients who have hypothyroidism and recommended that this is excluded before starting lipid–lowering therapy. Nephrotic syndrome is associated with increased total and LDL-cholesterol levels but can also increase statin toxicity as statins (which are mostly pro-drugs) are highly bound to albumin and low albumin levels predispose to muscle toxicity caused by the active free statin acids.

CG67 had included a general recommendation about consideration of dyslipidaemias. The scoping process had indicated that more guidance was required if possible for non-specialists in deciding which patients required more specialist care. NICE has produced guidance on who should be investigated for familial hypercholesterolaemia. As reviewed in NICE guideline CG71 relatives of index patients with familial hypercholesterolaemia have lower lipid levels than index cases. Recent evidence shows that index cases tend to be individuals with a larger number of LDL-cholesterol raising genetic polymorphisms.[256] The GDG felt the same considerations were likely to apply to other genetic hyperlipidaemias. The GDG considered it important to include a recommendation that the lipid profile, family history and clinical findings should be used when considering referral rather than use of strict cut-offs. The GDG considered that dyslipidaemias may be missed by undue reliance on strict cut-off limits and that non-experts should use methods such as email, choose & book advice, and telephone calls to seek advice to ensure these syndromes are identified. Referral for face to face consultation is not always required.

The GDG considered the changing nature of CVD in the UK over the last 20 years. The incidence of physical signs, for example tendon xanthomata and rates of CVD have fallen substantially. Many index cases for genetic hyperlipidaemias were likely to have been treated resulting in regression of physical signs and lack of CV event histories. The GDG noted the recommendation in the Joint British Societies guideline I for genetic assessment of patients with very high cholesterol levels even without family history (>9 mmol/litre).[6] This corresponded to a high score and probability of a genetic hyperlipidaemia in the Dutch Familial Hypercholesterolaemia scoring system.[51] The GDG considered that patients with a total cholesterol >9 mmol/litre were likely to include high proportions with unidentified genetic hyperlipidaemias or with rarer secondary causes of hyperlipidaemia which require specialist diagnostic advice.

The GDG discussed recommendations for people with raised triglycerides levels. The GDG noted that extreme triglyceride levels were associated with pancreatitis and a high risk of morbidity and mortality independent of CVD.[147] Registry data confirms a 20-fold excess risk of pancreatitis occurs in patients with lipoprotein lipase deficiency.[98,147] The GDG noted the Royal College of Pathologists' recommendation that triglycerides >20 mmol/litre were considered a laboratory result to be urgently reported to primary care. This value has been used extensively in international consensus statements. The GDG recommended that all patients with triglycerides >20 mmol/litre required urgent review by a lipid specialist if not caused by acute excess alcohol or poor glycaemic control.

The GDG considered the management of patients with triglycerides between 10 and 20 mmol/litre. Many of these patients have secondary causes of hypertriglyceridaemia. Triglycerides are subject to large biological variation which is amplified in post-prandial samples. The GDG recommended that fasting lipid specimen is taken within 5 days to obtain an accurate estimate of triglyceride levels. The GDG considered that in about 30% of people the result will be within normal limits. If triglycerides are still raised then advice should be sought from a lipid specialist about further management.

The GDG considered the clinical implications of triglycerides between 4.5 and 10 mmol/litre. In epidemiological studies these levels of elevated triglycerides are associated with excess CVD risk above that predicted using LDL cholesterol. Statins have been shown to reduce triglycerides in patients with these levels. The GDG recommended that environmental and lifestyle factors are optimised to reduce triglyceride levels. A proportion of these patients with elevated triglycerides and cholesterol will have a remnant hyperlipidaemia which would require specialist

	management. The presence of a non-HDL cholesterol >7.5 mmol/litre would identify many of these patients.

11.9 Research recommendations

3. 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.

4. 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 CV outcomes have recruited many people older than 80 years yet the important effect of age on CVD risk suggests that all people in this group should be offered statin therapy. However there is no evidence to validate the CVD benefits and side effects of statin therapy such as effect on muscle and renal function 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.

5. What is the effectiveness of statins or other LDL cholesterol-lowering treatments in people with type 1 diabetes?

Why this is important

People 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. Long term glycaemic control is associated with better outcomes but no trial has investigated the efficacy of statin therapy or other LDL-cholesterol-lowering therapies exclusively in people with type 1 diabetes.

6. 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 people 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 CV 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 CV 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.

11.10 Adherence to statin therapy

The development of statins has been heralded as an important advance in the primary and secondary prevention of CVD. Adherence to statin treatment has however been shown to decrease over time.

Continuation rates in the West of Scotland Coronary Prevention Study (WOSCOPS) were 84.5% patients after 1 year and this fell to 70.4% at 5 years.[237,237] Adherence in the real world is substantially worse than that seen in clinical trials. Adherence with statins declines over time and a significant proportion of patients stop taking their statin within 2 years of initiation. Patients with high adherence are less likely to be hospitalised than those with lower adherence and patients receiving statins for secondary prevention are more likely to adhere to therapy than those receiving them for primary prevention.[113] NICE has produced a guideline on Medicines Adherence.[188] The scope for this guideline included specific interventions for adherence to statin treatment.

11.10.1 Review question: What is the clinical and cost effectiveness of interventions to improve adherence to statin therapy for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

Table 65: PICO characteristics of review question

Population	Adults prescribed statins
Interventions	Coenzyme Q_{10} Vitamin D
Comparison	Placebo
Outcomes	Adherence Quality of life
Study design	RCTs, SRs of RCTs

For full details see review protocol in Appendix C.

11.10.2 Clinical evidence

Three RCTs were included in the review[33,46,288] which compared coenzyme Q_{10} (CoQ_{10}) with placebo. All studies recruited patients experiencing myalgia, and the studies assessed ongoing pain using one of the following instruments: a visual analogue scale (VAS),[33,288] the McGill Pain Questionnaire,[32,33] the Brief Pain Inventory, including Pain Severity Score (PSS) and Pain Interference Score (PIS).[46,46]

Table 66: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Follow up
Bookstaver 2012[32,33]	CoQ_{10} (plus statin) versus placebo (plus statin)	n=76	VAS score McGill Questionnaire	3 months
Caso 2007[46,46]	CoQ_{10} (plus statin) versus placebo (vitamin E plus statin)	n=32	PSS PIS	1 month
Young 2007[288,288]	CoQ_{10} (plus statin) versus placebo (plus statin)	n=44	Δ VAS score	3 months

Measure of pain:

- 10 cm visual analogue scale (VAS) score.

- Short-Form McGill Pain Questionnaire (this scale measures both sensory and affective domains, which are combined into a total score. The maximum score for the sensory subscale is 33 and is 12 for the affective subscale).

Table 67: Results of VAS (Bookstaver 2012[32,33])

	CoQ_{10} (n=40)		Placebo (n=36)		
Measurement period	**Patients (n)**	**Mean score (cm)**	**Patients (n)**	**Mean score (cm)**	**P value (as stated by authors)**
Baseline	40	6.0±2.2	36	5.9±2.0	0.94
1 month	34	3.9±2.2	32	4.0±2.2	0.97
2 month	31	3.8±2.2	30	3.8±2.7	0.96
3 month	27	3.2±2.3	26	3.1±2.2	0.94

Data are presented as mean±SD.

Table 68: Results of McGill Pain Questionnaire (Bookstaver 2012[32,33])

Measurement	**CoQ_{10} (n=40)**	**Placebo (n=36)**	**P value (as stated by authors)**
Total pain rating index			
Baseline	12	14	
1 month	7.5	9	0.39
2 month	4	7	0.27
3 month	5	4	0.57
Sensory pain rating index			
Baseline	10	11.5	
1 month	6.5	7.5	0.34
2 month	4	4.5	0.52
3 month	3	4	0.24
Affective pain rating index			
Baseline	2.5	2	
1 month	1	1	0.81
2 month	0	1	0.06
3 month	0	0	0.37

Data are presented as median values.

Adherence to statin therapy at the end of the study: 20 patients (50%) in the CoQ_{10} group, 12 patients (33%) in the placebo group.

Caso 2007[46,46]

Assessment of pain:

- Brief Pain Inventory questionnaire, which includes:
  - Four items to measure pain intensity, rated on a numeric scale of 0 (no pain) to 10 (pain as bad as you can imagine). Pain intensity was assessed by calculating a Pain Severity Score (PSS), computed by averaging the scores of the 4 pain intensity items.
  - Seven items to measure pain interference with daily life, rated on a numeric scale of 0 (does not interfere) to 10 (completely interferes). The impact of pain on daily living activities and wellbeing

was assessed by calculating a Pain Interference Score (PIS), obtained by averaging the ratings of the 7 interference items.

Table 69: Results of PSS and PSI (Caso 2007[46,46])

Measurement	CoQ_{10} (n=18)	Placebo (n=14)
PSS		
Baseline	5.00±0.34	4.39±0.60
1 month	2.97±0.48	4.73±0.68
PIS		
Baseline	4.31±0.50	4.74±0.52
1 month	2.82±0.61	4.25±0.70

Data are presented as mean±SD

Young 2007[288,288]

Measure of pain:

- VAS score: intensity of pain rated from 0 mm to 100 mm.

Table 70: Simvastatin dose tolerated at 12 weeks (Young 2007[288,288])

Tolerated dose (mg/day)	CoQ_{10} and simvastatin therapy (n=22)	Simvastatin alone (n=21)
40	16 (73%)	13 (59%)
20	0	3 (14%)
10	0	2 (9%)
0	6 (27%)	4 (18%)

Data are expressed as number (percentage) of patients.

Table 71: Changes in myalgia score and myalgia score adjusted for the number of affected sites from baseline to the end of study (Young 2007[288,288])

	CoQ_{10} and simvastatin therapy (n=22)	Simvastatin alone (n=21)	P value as stated by authors
Δ Myalgia score (mm)	6.0 (2.1–8.8)	2.3 (0–12.8)	0.63
Δ Myalgia score adjusted for number of affected sites (mm)	4.2 (1.0–6.4)	2.1 (0–11.4)	0.73

Data are expressed as median (interquartile range). Myalgia scores ranged from 0 (no pain) to 100 (worst pain).

Adherence to simvastatin was 98% in the 2 groups, and adherence to CoQ_{10} was 93%.

Table 72: CoQ_{10} versus placebo: quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
VAS score[32,33]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	No serious imprecisions
McGill Questionnaire[32,33]	1	RCT	Serious[(a)]	No serious inconsistency	Serious indirectness [(b)]	Not estimable because

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
						non-parametric statistics were reported
PSS[46,46]	1	RCT	Serious[(a)]	No serious inconsistency	Serious indirectness [(b)]	No serious imprecisions
PIS[46,46]	1	RCT	Serious[(a)]	No serious inconsistency	Serious indirectness [(b)]	No serious imprecisions
Δ VAS score[288,288]	1	RCT	Very serious limitations[(c)]	No serious inconsistency	Serious indirectness [(b)]	Not estimable because non-parametric statistics were reported

(a) Selection bias
(b) Study reported pain, which is a surrogate outcome for adherence and quality of life.
(c) Study did not report use of analgesia in either intervention or placebo arm.

Table 73: CoQ_{10} versus placebo: clinical summary of findings

Outcome	CoQ_{10}	Placebo	Absolute effect	Quality
VAS score[32,33]	40	36	MD 0.1 higher (0.94 lower to 1.14 higher)	Low
McGill Questionnaire[32,33]	40	36	Not estimable[a]	Low
PSS[46,46]	18	14	MD 1.76 lower (2.18 to 1.34 lower)	Low
PIS[46,46]	18	14	MD 1.89 lower (1.89 to 0.97 lower)	Low
Δ VAS score[288,288]	22	21	Not estimable[a]	Very Low

(a) Not estimable because non-parametric statistics were reported.

11.10.3 Economic evidence

Published literature

No relevant economic evaluations were identified that compared coenzyme Q_{10} or vitamin D with placebo for improving adherence to statin therapy in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease. See also the economic article selection flow chart in Appendix E.

11.10.4 Evidence statements

Clinical

- One study with 76 people on statin therapy showed that there is no difference in reducing myalgia (pain measured with VAS score) in people treated with CoQ_{10} or placebo. [Moderate quality]
- One study with 32 people on statin therapy suggested that CoQ_{10} is more clinical effective than placebo in reducing myalgia (pain measures with PSS and PSI). [Moderate quality]
- One study with 76 people showed that after 3 months adherence to statin therapy at the end of the study was 50% in the CoQ_{10} group and 33% in the placebo group. [Moderate quality]
- One study with 44 patients showed that after 3 months adherence to statin therapy was 98% in both the CoQ_{10} and placebo groups. [Very low quality]

Economic

- No relevant economic evaluations were identified.

11.10.5 Recommendations and link to evidence

Adherence to statin therapy

Recommendation	79. Do not offer coenzyme Q_{10} or vitamin D to increase adherence to statin treatment. [new 2014]
Relative values of different outcomes	The GDG was willing to accept any measure of adherence but the studies available did not measure adherence. The GDG agreed to inclusion in the review of studies with surrogate markers, for example whether pain improved, and these were mainly numerical scales.
Trade-off between clinical benefits and harms	The studies of coenzyme Q_{10} were short studies with a small number of participants and did not provide adequate evidence of benefits. No evidence was found on the use of Vitamin D.
Economic considerations	No relevant economic evidence was identified. The GDG concluded that there is no clinical evidence in favour of benefit from the use of coenzyme Q_{10}. Hence the intervention would not be cost effective. It is noted than coenzyme Q_{10} is listed in BNF as available for prescription (indicated for children with mitochondrial disorders), but can only be obtained from special-order manufacturers or importers. No list price is given. It can alternatively be purchased over-the-counter by individuals from pharmacies and other shops. There is no clinical or economic evidence regarding vitamin D, and so no judgement can be made on its cost effectiveness for increasing adherence.
Quality of evidence	Overall the quality of the evidence is low or very low, as all the included studies had statistical and design limitations. In addition, the studies were not powered to detect significant differences.
Other considerations	The GDG considered that adherence to statins is a significant clinical problem but that the evidence review did not provide sufficient evidence to make a specific recommendation. The studies concentrated on the reduction of muscle pain when taking a statin with coenzyme Q_{10}. The GDG considered however that while muscle pain may be a problem for some people, adherence is a common problem with all medications. Statins are prescribed long term and it is also likely that the issues relevant to people taking statins will change over time. Regular review and discussion is therefore required.

	The GDG agreed that the general measures to improve adherence outlined in the NICE Medicines adherence guideline[188] should be used; these include providing the patient with information, accepting that non-adherence happens and exploring why, and addressing problems patient may have in taking medicine. The recommendations in the Medicines adherence guideline make clear that some people make a choice not to take medicines and this should be respected. Coenzyme Q_{10} and vitamin D are not indicated for this usage.

11.11 Advice and monitoring for adverse effects

Statins are widely prescribed medicines, yet like all medicines they may be associated with adverse events. A wide variety of adverse events have been described with statins. Some adverse effects such as myalgia are symptoms reported by patients, others such as abnormal liver function tests and development of diabetes require biochemical monitoring. The GDG was interested in whether it was possible to predict who might develop adverse effects as this might inform advice to patients and modify the frequency and targeting of monitoring.

11.11.1 Review question: Who is at risk of adverse effects from statin treatment? (Are some subgroups at different risk of adverse events?)

For full details see review protocol in Appendix C.

The objective of this review was to determine if there are any specific groups who are at higher risk of adverse events amongst the population of patients receiving statin therapy. The GDG therefore agreed that studies which included patients who were all on statin therapy were the best source of evidence for answering this question.

However, the GDG also agreed that studies which compared the risk of adverse events between statins and placebo could provide evidence to address the question on which subgroup of patients receiving statin therapy for primary prevention were at higher risk of adverse events. The clinical review therefore also included these studies.

The GDG classified the adverse events in decreasing order of importance and identified the key confounders for each outcome as follows:

Table 74: Key confounders

Serial no.	Outcome	Key confounders
1.	Rhabdomyolysis (CK more than 10 times normal level)	Age, gender, renal impairment, history of muscle pain with another lipid lowering therapy (LLT), unexplained cramps, history of elevated creatine kinase (CK), family history of muscular symptoms, family history of muscular symptoms with LLT, hypothyroidism, duration of statin treatment more than 3 months, treatment with antidepressant, type of statin
2.	New-onset diabetes	Age, fasting glucose, body mass index (BMI), white blood cell count (WBC), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, HDL cholesterol, triglyceride, sex, smoking, hypertension, use of statins during screening, use of beta-blockers, treatment with atorvastatin, family history of diabetes, ethnicity, polycystic ovarian disease, gestational diabetes
3.	Liver (transaminases more than 3 times normal level)	-
4.	Myalgia	Age, gender, renal impairment, history of muscle pain with another LLT, unexplained cramps, history of elevated CK, family history of muscular symptoms, family history of muscular symptoms with LLT, hypothyroidism, duration of statin treatment more than 3 months, treatment with antidepressant, type of statin

11.11.2 Clinical evidence

We searched for studies reporting multivariable prognostic analysis of the predictors of adverse events in patients on statin therapy.

Five studies were included in the clinical evidence review.[37,39,114,230,271] As the populations included in the studies were different, the data were not pooled. Instead, trends in the data were analysed.

See Table 2 for the summary of studies included in the review.

Evidence from these are summarised in the quality assessment table (see Table 3) and summary of findings tables for each of the outcomes. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 75: Summary of studies included in the review

Study	Population	Key confounders reported	Outcome	Comments
Studies comparing all patients receiving statin therapy				
Bruckert et al. 2005[37,37] PRIMO study	Patients receiving high dose statin therapy n=7294 Setting: GP practices, France	History of muscle pain with another LLT, unexplained cramps, history of elevated CK, family history of muscular symptoms, family history of muscular symptoms with LLT, hypothyroidism, duration of statin treatment more than 3 months, treatment with antidepressant, type of statin	Muscular pain (myalgia)	-
Waters et al. 2011[270,271]	Study reports results from 3 separate trials; 2 trials were included in this review. **TNT trial:** (n=7595) Patients randomised to receive either atorvastatin 80 mg or atorvastatin 10 mg. **IDEAL trial:** (n=7461) Patients were randomised to receive either atorvastatin 80 mg or simvastatin 20 mg **SPARCL trial:** (n=3803) Patients were randomised to receive atorvastatin 80 mg or placebo. This trial was not included in this review as not all patients were on statin therapy.	Age, fasting glucose, BMI, WBC, SBP, DBP, total cholesterol, HDL cholesterol, triglyceride, sex, smoking, hypertension, use of statins during screening, use of beta-blockers, treatment with atorvastatin	New-onset diabetes	Studies did not account for family history of diabetes, ethnicity, polycystic ovarian disease, gestational diabetes
Studies comparing statins with placebo				
Buettner et al. 2008[39,39]	Cross sectional analysis using data from NHANES, USA Population included those over 40 years of age without a diagnosis of	Age, sex, race, ethnicity, educational level, physical activity, alcohol intake, coronary heart disease,	Musculo-skeletal pain	Did not account for History of muscle pain

Study	Population	Key confounders reported	Outcome	Comments
	arthritis n=3580	diabetes, cancer, systolic blood pressure, ABI, BMI, total cholesterol, smoking, health status		with another LLT, renal impairment, family history of muscular symptoms, duration of statin treatment, type of statin
Sattar et al. 2010[230,230]	Meta-analysis of trials comparing statins with placebo.	Age, BMI, change in LDL-cholesterol concentration	New-onset diabetes	Meta-regression of 3 risk factors to explain heterogeneity
Hippisley-Cox and Coupland 2010 [114]	Prospective cohort study using routinely collected data from 368 GP practices in England and Wales (QResearch database) n=2,004,692	Accounts for type and dose of statin in final analysis.	Rhabdo myolysis, Liver dysfunction	Does not list potential confounding variables accounted for in initial analysis

LLT: lipid lowering therapy; CK: creatine kinase; NHANES: National Health and Nutrition Examination Survey; ABI: Ankle Brachial Index; BMI: Body Mass Index

Table 76: Quality assessment of included studies

Study	Quality assessment – methodological flaws of studies						
	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Important confounders accounted for	Appropriate statistical analysis	Quality
Bruckert et al. 2005[37,37]	✓	✓	✓	✓	✓(a)	✓	Moderate
Waters et al. 2011[270,271]	✓	✓	✓	✓	×(b)	✓	Moderate
Buettner et al. 2008[39,39]	✓	✓	×(c)	×(d)	✓	✓	Low
Sattar et al. 2010[230,230]	✓	✓	×(e)	✓	×(f)	✓	Low
Hippisley-Cox and	✓	✓	✓	×(g)	✓(h)	✓	Moderate

Study	Quality assessment – methodological flaws of studies						
Coupland 2010 [114]							

(a) Difference in mean percentage body fat mass between groups, lower in group reporting muscular symptoms
(b) Studies did not account for family history of diabetes, ethnicity, polycystic ovarian disease, gestational diabetes as key confounding factors. One study (SPARCL) compared statins to placebo.
(c) Cross sectional analysis using data form National Health and Nutrition Examination survey; not designed as part of a cohort study
(d) Outcomes (CHD, diabetes, cancer) were defined by patients self-reporting of diagnosis, records not checked
(e) Study not designed to be a prognostic study (meta-analysis of trials), not other confounding factors reported except 3 outlined in meta-regression analysis
(f) Meta-regression analysis for 3 factors to explain residual heterogeneity between trials- basis not clear, also not clear why analysis did not include any other confounding factors.
(g) QResearch database based study, possible misclassification and ascertainment of outcomes
(h) Study mentions all relevant predictors of outcomes were included in the analysis, but does not list them.

11.11.2.1 Myalgia

One study evaluated predictors of myalgia in patients receiving high dose statin therapy.[37,37] Age, gender and BMI were not identified as risk factors for muscular symptoms. Effect sizes of risk factors which were identified as independent predictors of myalgia on multivariate analysis are summarised in Table 77. See also forest plot D.1.1.

One study evaluated whether statin use was associated with higher prevalence of musculoskeletal pain.[39,39] The study presented odds ratios for musculoskeletal pain different regions (neck/upper back/upper extremities/lower back/ lower extremities/any region). The findings are summarised in Table 78.

Table 77: Summary of findings: Myalgia (all patients on statin therapy)[37,37]

Risk factors	Odds ratio (95% CI) for independent predictors of myalgia	P value
History of muscle pain with another LLT	10.12 [8.23,12.45]	<0.0001
Unexplained cramps	4.14 [3.46, 4.95]	<0.0001
History of elevated CK	2.04 [1.55, 2.68]	<0.0001
Family history of muscular symptoms	1.93 [1.10, 3.34]	0.022
Family history of muscular symptoms with LLT	1.89 [1.12, 3.17]	0.017
Hypothyroidism	1.71 [1.10, 2.65]	0.017
Duration of statin treatment more than 3 months	0.28 [0.21, 0.37]	<0.0001
Treatment with antidepressants	0.51 [0.35, 0.74]	0.0004
Type of statin(a)		
Atorvastatin	1.28 [1.02, 1.60]	0.035
Simvastatin	1.78 [1.39, 2.29]	<0.0001
Fluvastatin XL	0.33 [0.26, 0.42]	<0.0001

(a)Odds ratios were calculated using pravastatin as the reference
Abbreviations-LLT: lipid lowering therapy; CK: creatine kinase

Table 78: Summary of findings: Myalgia (statins users versus non-users)[39,39]

Risk factors (outcomes)	Odds ratio (95% CI)	P value

Risk factors (outcomes)	Odds ratio (95% CI)	P value
Any region	1.50 [1.07, 2.11](a)	0.01
Lower extremity pain		
Statin with Coronary heart disease (b)	4.59 [1.22, 17.26]	
Statin without Coronary heart disease	1.04 [0.58, 1.86]	0.06 (p value interaction)
Females on statin therapy	2.06 [1.07, 3.97]	
Males on statin therapy	1.12 [0.64, 1.96]	0.06 (p value interaction)

(a) Adjusted for age, sex, race, smoking status, self-reported health coronary heart disease, diabetes, cancer, systolic blood pressure, BMI, total cholesterol, ankle brachial index

(b) Independent predictor, associated with pain in lower extremities but not in other regions

11.11.2.2 New-onset diabetes

One study reported findings from 3 RCTs on the risk of new-onset diabetes in patients receiving statin therapy.[270,271] Two of these RCTs compared the incidence in patients receiving high and low dose statin therapy (TNT, IDEAL). Table 79 presents the hazard ratios for risk factors which were identified as independent predictors on multivariate analysis. The third RCT (SPARCL) compared the incidence of new-onset diabetes in patients receiving statin therapy with placebo. Findings form this study are summarised in Table 80. See also forest plots D.1.2 and D.2.3 (Figure 7)

An independent meta-analysis compared the incidence of new-onset diabetes in statins with placebo and evaluated the incidence by the type of statin.[230,230] This meta-analysis included 13 trials. The findings of this meta-analysis echo the findings of the previous review on adverse events of statins (Section 11.11). See also forest plots (Appendix I). An exploratory meta-regression analysis of baseline age, baseline BMI and change in LDL cholesterol during treatment was also undertaken. Meta-regression indicated a stronger association between statin therapy and new-onset diabetes in older participants (p=0.019), but the association was not significant for baseline BMI (p=0.177) and percentage change in LDL cholesterol concentration (p=0.102).

Table 79: Summary of findings: New-onset diabetes (all patients on statin therapy)

Risk factors	Study[270,271]	Hazard ratio (95% CI) for independent predictors of new-onset diabetes	P value
Fasting glucose per 10 mg/dl increase	TNT	2.53 [2.34, 2.73]	<0.0001
	IDEAL	2.49 [2.26, 2.74]	<0.0001
BMI per 3 kg/m^{2}increase	TNT	1.21 [1.16, 1.26]	<0.0001
	IDEAL	1.29 [1.20, 1.38]	<0.0001
Natural log [WBC] per 0.25 log (103/mm^3) increase	TNT	1.15 [1.06, 1.24]	0.0012
Natural log [triglyceride] per 1.0 log (mg/dl) increase	TNT	1.85 [1.53, 2.22]	<0.0001
	IDEAL	1.48 [1.19, 1.83]	0.0004
Hypertension	TNT	1.24 [1.05, 1.46]	0.0098
	IDEAL	1.32 [1.09, 1.60]	0.005
Treatment with atorvastatin 80 mg	TNT	1.10 [0.94, 1.29]	0.226
	IDEAL	1.19 [0.98, 1.43]	0.075

Table 80: Summary of findings: New-onset diabetes (statins users versus non-users)

Risk factors	Study[27] 0,271	Hazard ratio (95% CI)	P value
Fasting glucose per 10 mg /dl increase	SPARCL	1.96 [1.74, 2.20]	<0.0001
BMI per 3 kg/m^{2}increase	SPARCL	1.19 [1.11, 1.27]	<0.0001
Natural log [triglyceride] per 1.0 log (mg/dl) increase	SPARCL	2.51 [1.92, 3.29]	<0.0001
Hypertension	SPARCL	1.42 [1.08, 1.86]	0.012
Treatment with atorvastatin 80 mg	SPARCL	1.37 [1.08, 1.75]	0.011

11.11.2.3 Rhabdomyolysis

One study compared the incidence of rhabdomyolysis in statins with placebo and presented hazard ratios by the type and dose of statin used.[114] Table 81 summarises the findings. See also forest plots (Appendix I).

Table 81: Summary of findings: Rhabdomyolysis (statins users versus non-users)

Statin (type and dose)	Hazard ratio (95 % CI)- Females (a)	Hazard ratio (95 % CI)- Males (a)
Simvastatin 10/20 mg/day	2.91 (2.19 to 3.88)	6.12 (4.97 to 7.55)
Simvastatin 40/80 mg/day	3.30 (2.32 to 4.69)	6.11 (4.79 to 7.80)
Atorvastatin 10 mg/day	2.98 (2.09 to 4.26)	6.11 (4.70 to 7.93)
Atorvastatin 20/40/80 mg/day	2.62 (1.42 to 4.84)	8.18 (5.82 to 11.50)
Fluvastatin 20 mg/day	Insufficient data	11.86 (4.88 to 28.85)
Fluvastatin 40/80 mg/day	Insufficient data	1.20 (0.17 to 8.53)
Pravastatin 10/20 mg/day	2.60 (0.96 to 7.04)	3.62 (1.49 to 8.78)
Pravastatin 40 mg/day	2.68 (0.99 to 7.25)	5.79 (3.07 to 10.91)
Rosuvastatin all	5.41 (2.64 to 11.07)	4.19 (1.86 to 9.45)

(a) Adjusted for established risk factors or existing risk prediction scores. Risk factors adjusted for not outlined.

11.11.2.4 Liver dysfunction (transaminases more than 3 times normal level)

One study compared the incidence of liver dysfunction in statins with placebo and presented hazard ratios by the type and dose of statin used.[114] Table 82 summarises the findings. See also forest plot (Appendix I).

Table 82: Summary of findings: Liver dysfunction (statins users versus non-users)

Statin (type and dose)	Hazard ratio (95 % CI)- Females (a)	Hazard ratio (95 % CI)- Males (a)
Simvastatin 10/20 mg per day	1.47 (1.32 to 1.63	1.39 (1.25 to 1.54)
Simvastatin 40/80 mg per day	1.62 (1.41 to 1.86)	1.79 (1.60 to 2.01)
Atorvastatin 10 mg per day	1.37 (1.19 to 1.58)	1.45 (1.27 to 1.65)
Atorvastatin 20/40/80 mg per day	2.00 (1.64 to 2.44)	1.86 (1.55 to 2.24)
Fluvastatin 20 mg per day	1.64 (0.88 to 3.06)	1.20 (0.60 to 2.40)
Fluvastatin 40/80 mg per day	3.08 (2.14 to 4.43)	2.37 (1.66 to 3.38)
Pravastatin 10/20 mg per day	1.06 (0.68 to 1.67)	1.31 (0.90 to 1.92)

Statin (type and dose)	Hazard ratio (95 % CI)- Females (a)	Hazard ratio (95 % CI)- Males (a)
Pravastatin 40 mg per day	1.91 (1.37 to 2.65)	1.13 (0.78 to 1.62)
Rosuvastatin all	1.31 (0.87 to 1.97)	1.46 (1.01 to 2.11)

(a) Adjusted for established risk factors or existing risk prediction scores. Risk factors adjusted for not outlined.

11.11.3 Economic evidence

Published literature

No relevant economic evaluations were identified that examined who is at risk of adverse effects from statin treatment in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease. See also the economic article selection flow chart in Appendix E.

11.11.4 Evidence statements

Clinical

- One study with (n=7294), in a multivariable analysis, suggested that people with a history of muscle pain with another LLT or with unexplained cramps may be at higher risk of myalgia when taking a statin than people without a history of muscle pain with another LLT or without unexplained cramps. [Moderate quality]
- Three studies (n=18,859) suggested that statin therapy increase the risk of new-onset diabetes, but there is uncertainty. [Moderate quality]
- One study (n=2,004,692) suggested that statin therapy increase the risk of rhabdomyolysis and liver dysfunction. [Moderate quality]

Economic

- No relevant economic evaluations were identified.

11.11.5 Recommendations and link to evidence

Advice and monitoring for adverse effects

Recommendations	**80. Advise people who are being treated with a statin:** • **that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins and** • **to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements. [new 2014]** **81. Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses. [new 2014]** **82. Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.** • **If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment.** • **If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose. [new 2014]** **83. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase. [2008]** **84. If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than 3 months. [new 2014]** **85. Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. [2008]** **86. Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin. Measure liver transaminase within 3 months of starting treatment and at 12 months, but not again unless clinically indicated. [2008]** **87. Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal. [2008]** **88. Do not stop statins because of an increase in blood glucose level or**

	HbA_{1c}. (See the recommendations on assessing for risk of diabetes mellitus in Preventing type 2 diabetes [NICE public health guidance 38].) [new 2014] **89.Statins are contraindicated in pregnancy:** • **Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility.** • **Advise women planning pregnancy to stop taking statins 3 months before they attempt to conceive and to not restart them until breastfeeding is finished. [new 2014] [This recommendation updates and replaces recommendation 1.10.1.7 from Type 2 diabetes (NICE clinical guideline 87).]**
Relative values of different outcomes	These recommendations were informed by the evidence review of statin efficacy, the evidence review on prediction of adverse effects of statins, and the evidence review on interventions to increase adherence to statins. Changes in lipid sub-fractions in trials after starting statin therapy also informed these recommendations. Changes in safety-related biomarkers in trials after starting statin therapy were considered a key outcome. Requirements from summary of product characteristics (SPC) were also taken into account.
Trade-off between clinical benefits and harms	Identification of people most likely to suffer from adverse events would help target monitoring and reduce adverse events. While blood tests may not be a significant harm, they can cause discomfort to patients and reducing the monitoring required for those at least risk would benefit patients. Harms identified include raised blood sugar and potential development of diabetes. This risk is small but clear. The evidence suggests that effect of the statin is to bring forward the development of diabetes in those at risk. Patients with type 2 diabetes are however at greater CV risk, and so have a high potential to benefit from statins.
Economic considerations	No relevant economic evidence was identified. Providing statin treatment to those who have a high risk of reacting to it and incurring an adverse event is not in the clinical interests of patients and also incurs costs of treating the adverse event, and so would not be cost effective. Hence it is appropriate not to recommend treatment to any groups believed to be at high risk of adverse events, particularly any which are serious or long-lasting. If a patient has a low risk of a short-term adverse event which would cease on stopping taking statins and which does not require significant additional treatment (such as myalgia or raised liver transaminases), then this would not constitute a reason not to recommend statins on economic grounds, as the minority who incur such an event could be advised to change statin or cease treatment (at which point they cease to benefit from statins, but also cease to incur side effects or any costs of treating them), whilst the majority who experience no adverse event could continue to take and benefit from statins. Raised rates of new-onset diabetes do increase the cost of statin treatment. However, in the GDG's opinion this is most likely to represent only a bringing forward of diagnosis of type 2 diabetes which the individuals concerned would be expected to otherwise develop at a later point. The excess cost is therefore the cost of treating the person for a few extra years.
Quality of evidence	High to moderate quality evidence was found for safety end points in CVD outcome studies with statins. Evidence for myalgia varied from high to low quality. The majority of evidence for adverse liver events was of high or moderate quality. Evidence for new-onset diabetes was of high or moderate quality. The studies were underpowered for the rare adverse event outcome of rhabdomyolysis and the quality of evidence for this outcome varied from high to very low (see Sections 11.3

	and 11.3.1 on the efficacy of statin therapy). Poor quality evidence was found for factors predisposing to increased rates of side effects with statin therapy (see Section 11.11.2 on the prediction of adverse events).
Other considerations	**Drug interactions** The GDG reviewed the adverse event monitoring required in statin SPCs. The GDG noted that many statins showed pharmacokinetic interactions with other drugs, food components (such as grapefruit juice) or supplements (St John's wort) that were metabolised through the cytochrome P450 3A4 pathway. According to the SPC, statins are also contraindicated in pregnancy. The GDG recommended that patients were informed of these potential drug interactions and were advised to review the drug safety information provided to them or how to they might access such information. The GDG was mindful that some drugs (for example, macrolide antibiotics) interact with statins but might be required in acute management of infections or other acute conditions. The GDG considered that patients should restart their statin as soon as practical after conclusion of a course of these drugs and that they should be reminded of this. **Myalgia and rhabdomyolysis** The GDG discussed the requirement for screening for muscle symptoms and measurement of creatine kinase with statin therapy. The GDG noted the low level of specific myositis or rhabdomyolysis associated with statin therapy in clinical trials, and the poor correlation between symptoms of myalgia and elevations in creatine kinase. The GDG recommended that patients with prior muscle symptoms, especially if associated with previous lipid-lowering therapy, required assessment of creatine kinase levels. These patients needed to be initiated at lower doses of statin if creatine kinase levels were elevated. The GDG considered that most cases of statin-induced myopathy occurred on initiation of therapy. The GDG recommended that other causes of muscle pain be sought in patients that had been established on statin therapy for 3 months or more. **Liver dysfunction** The GDG discussed evidence for hepatotoxicity with statins and the requirement for monitoring transaminases in the drug licences. The GDG noted that transaminase elevations are very frequent in the population and that both raised transaminases and gamma-glutamyl transferase had been identified as CVD risk factors in the context of non-alcoholic fatty liver disease or metabolic syndrome.[101] The GDG decided that statin therapy should not be withheld unless transaminases exceeded the levels mandated for non-initiation or cessation (more than 3 times the upper limit of normal) or for changes in drug doses. SPCs for statins indicate that is transaminases are more than 5 times the upper limit of normal, the test should be repeated and if the level remains this high than statins should not be used. If the repeated level is less than t times the upper limit of normal, a lower dose of atorivastatin should be used. The GDG noted that transaminase elevations usually occurred on initiation of statin therapy. The GDG recommended that transaminases were measured 3 months after initiation and then yearly thereafter unless there other hepatic comorbidities existed that required more frequent monitoring. **New-onset diabetes** The evidence reviews showed an increase in new-onset diabetes with statin therapy but a clear relationship with statin dose or intensity of statin therapy could not be established. The elevations in glucose or HbA_{1c} produced by statin therapy in the trials were small. The GDG reviewed the evidence from one randomised controlled trial of statin therapy that had identified the risk factors associated with new cases of diabetes. The patients that developed diabetes had pre-existing risk factors for the condition including features associated with the metabolic syndrome. The GDG noted that patients with the metabolic syndrome were at increased CVD risk. The GDG recommended that as the CVD benefits of statin therapy exceeded the risks due

	to glucose elevation, statin therapy should not be stopped due to acute elevations in blood glucose. **Pregnancy** The previous type 1 diabetes guideline had included a recommendation about potential risk associated with statin treatment in pregnancy and that statin treatment be discontinued if pregnancy was a possibility. The recommendation was re-worded to provide more information.

12 Fibrates for the prevention of CVD

12.1 Introduction

Fibrates are a diverse group of pharmacological compounds that include gemfibrozil, fenofibrate, ciprofibrate and bezafibrate. Their primary action is to act as activators of peroxisomal proliferator-activated receptor alpha (PPAR-α). Activation of this genetic regulatory element leads to reduction in plasma levels of triglycerides and drug-specific actions on other elements of the lipid profile and other CV biomarkers.[277,278] Most fibrates (except gemfibrozil) raise HDL cholesterol; their actions on LDL cholesterol vary depending on baseline triglyceride levels and the specific drug. Fibrates have been used in clinical trials in CVD since 1970 as monotherapy. Given their actions in improving the atherogenic lipid triad (high triglycerides, low HDL cholesterol, and presence of small dense LDL-cholesterol particles) associated with type 2 diabetes, they have lately been used specifically in that context either as monotherapy or as a potential add-on to statins. They are not generally used clinically except in the treatment of very severe hypertriglyceridaemia.[264,264]

12.2 Review question: What is the clinical and cost effectiveness of fibrates versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

For full details see review protocol in Appendix C.

Table 83: PICO characteristics of review question

Population	Adults (18 years and over) without established CVD and: • At risk of CVD • Type 1 diabetes • Type 2 diabetes • Chronic kidney disease Adults (18 years and over) with established CVD including: • Prior myocardial infarction • Acute coronary syndromes (STEMI, NSTEMI or unstable angina) • Stable angina • Stroke • Peripheral artery disease
Interventions	• Fibrates versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Fibrates (plus statins) versus statins • Fibrates (no statin) versus placebo (no statin)
Comparisons	Statin or placebo
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • Myocardial infarction • Stroke or TIA (transient ischaemic attack) • Hospitalisation • Adverse events

	• Quality of life
Study design	RCT, SRs of RCTs

12.3 Clinical evidence

Nine studies were identified.[11,30,31,87,93,94,103-105,107,124,131,152,167,225-227,251,252] Three studies were in people with type 2 diabetes with and without prior CVD.[11,31,103-105,107,124,131,251,252] Two of these studies compared fibrate versus placebo[11,124,131,251,252] and the other compared fibrate plus statin versus statin.[31,103-105,107] Five studies were identified for secondary prevention comparing fibrate versus statin.[30,87,94,167,225-227]

Table 84 summarises the studies. Evidence from these are summarised in the clinical GRADE evidence profile (Table 85). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

No studies were identified that reported separate information on black and minority ethnic groups or women or people with a family history of CVD, autoimmune disease, serious mental illness or people in low socioeconomic groups.

Table 84: Summary of studies included in the review

Study	Intervention, comparison	Population	Outcomes	Follow up time	Comments
BIP 2000[30,30]	Bezafibrate versus placebo	n=3090 men and women with CAD, 10% of participants had diabetes Israel	All-cause mortality Non-fatal myocardial infarction Stroke	6.2 years	Secondary prevention
Ericsson 1996[87,87] BECAIT	Bezafibrate versus placebo	n=92 men who had survived myocardial infarction Sweden	Sudden cardiac death	5 years	Secondary prevention
Frick 1987[93,152] Helsinki Heart Study	Gemfibrozil versus placebo	n=4801 men Finland	All-cause mortality Sudden cardiac death Non-fatal myocardial infarction	5 years	Primary prevention
Frick 1997[93,94] LOCAT	Gemfibrozil versus placebo	n=395 men, post-coronary artery bypass surgery Finland	All- cause mortality	2.8 years	Secondary prevention
Ginsberg 2010[31,103-105,107] ACCORD	Fenofibrate + simvastatin versus Placebo + simvastatin	n=5518 men and women with type 2 diabetes; average dose of simvastatin 22.3 mg in fenofibrate group, 22.4 mg in placebo group Canada, USA	All-cause mortality CV mortality Non-fatal myocardial infarction Stroke	4.7 years	Primary and secondary prevention, 37% of participants had prior CV event
Keech 2005[11,124,131] FIELD	Fenofibrate versus placebo	n=9795 men and women with and without CVD	All-cause mortality CV mortality Non-fatal myocardial	Median 5 years	Primary and secondary prevention, 22%

Study	Intervention, comparison	Population	Outcomes	Follow up time	Comments
		Multiple countries	infarction Sudden cardiac death Stroke Raised alanine aminotransferase (more than 3 times the upper limit of normal) Raised creatine phosphokinase (more than 10 times the upper limit of normal)		of participants had prior CV event, 94% people in the placebo group started statin therapy during study, 94% people in the fibrate group started statin therapy during study
Meade 2002[166,167] LEADER	Bezafibrate versus placebo	n=1568 men with lower extremity arterial disease, 17.1% of participants had diabetes UK	All-cause mortality CV mortality Stroke	4.6 years	Secondary prevention
Rubins 1999 [225-227] VA-HIT	Gemfibrozil versus placebo	n=2531 men with coronary heart disease, 24.5% of participants had diabetes USA	All-cause mortality Non-fatal myocardial infarction Stroke Hospitalisation	5.1 years	Secondary prevention
Steiner 2001[251,252] DAIS	Fenofibrate versus placebo	n=418 men and women with type 2 diabetes with or without previous coronary intervention Multicentre	All-cause mortality	3.5 years	Primary and secondary prevention, 48% of participants had a history of CAD

Table 85: Clinical evidence profile: fibrate versus placebo and fibrate plus statin versus statin for prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrates combined data	Control	Relative (95% CI)	Absolute		
All-cause mortality - Combined studies[11,30,31,93,94,103-105,107,124,131,152 167,225-227,251,252]												
8	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1173/13698 (8.6%)	1162/13675 (8.5%)	RR 1.01 (0.94 to 1.09)	1 more per 1000 (from 5 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality - Primary prevention; fibrate versus placebo[93,152]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	45/2051 (2.2%)	42/2030 (2.1%)	RR 1.06 (0.7 to 1.61)	1 more per 1000 (from 6 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - Mixed primary and secondary prevention - diabetes; fibrate versus placebo[11,124,131,251,252]												
2	randomised trials	serious[c]	no serious inconsistency	serious[d]	serious[e]	none	362/5102 (7.1%)	332/5111 (6.5%)	RR 1.1 (0.95 to 1.28)	6 more per 1000 (from 3 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality - Mixed primary and secondary prevention; fibrate + statin versus statin[31,103-105,107]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	203/2765 (7.3%)	221/2753 (8%)	RR 0.91 (0.76 to 1.1)	7 fewer per 1000 (from 19 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Secondary prevention; fibrate versus placebo[30,94,167,225-227]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	563/3780 (14.9%)	567/3781 (15%)	RR 0.99 (0.89 to 1.1)	1 fewer per 1000 (from 16 fewer to 15 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality– Combined[11,31,103-105,107,124,131,167]												

3	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	303/8443 (3.6%)	306/8438 (3.6%)	RR 0.99 (0.85 to 1.16)	0 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality – Mixed primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	serious[e]	none	140/4895 (2.9%)	127/4900 (2.6%)	RR 1.1 (0.87 to 1.4)	3 more per 1000 (from 3 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
CV mortality – Mixed primary and secondary; fibrate + statin versus statin[31,103-105,107]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[g]	none	99/2765 (3.6%)	114/2753 (4.1%)	RR 0.86 (0.66 to 1.13)	6 fewer per 1000 (from 14 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
CV mortality – Secondary prevention; fibrate versus placebo[166,167]												
1	randomised trials	very serious[h]	no serious inconsistency	no serious indirectness	very serious[b]	none	64/783 (8.2%)	65/785 (8.3%)	RR 0.99 (0.71 to 1.37)	1 fewer per 1000 (from 24 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Non-fatal MI – Combined [30,30 11,31,93,103-105,107,124,131,152,225-227]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[g]	none	667/12523 (5.3%)	810/12492 (6.5%)	RR 0.82 (0.74 to 0.91)	12 fewer per 1000 (from 6 fewer to 17 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI – Primary prevention; fibrate versus placebo[93,152]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[i]	none	40/2051 (2%)	61/2030 (3%)	RR 0.65 (0.44 to 0.96)	11 fewer per 1000 (from 1 fewer to 17 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal MI – Mixed primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	serious[g]	none	158/4895 (3.2%)	207/4900 (4.2%)	RR 0.76 (0.62 to 0.94)	10 fewer per 1000 (from 3 fewer to 16 fewer)	⊕⊕OO LOW	CRITICAL
Non-fatal MI – Mixed primary and secondary prevention; fibrate + statin versus statin[31,103-105,107]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	173/2765 (6.3%)	186/2753 (6.8%)	RR 0.93 (0.76 to	5 fewer per 1000 (from 16 fewer to 9	⊕⊕⊕⊕ HIGH	CRITICAL

									1.13)	more)		
Non-fatal MI – Secondary prevention; fibrates versus placebo[30,225-227]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[g]	none	296/2812 (10.5%)	356/2809 (12.7%)	RR 0.83 (0.72 to 0.96)	22 fewer per 1000 (from 5 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Sudden cardiac death – Combined[93,152]Ericsson 1996 BECAIT[11,124,131]												
3	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[j]	none	74/6993 (1.1%)	57/6975 (0.82%)	RR 1.3 (0.92 to 1.82)	2 more per 1000 (from 1 fewer to 7 more)	⊕OOO VERY LOW	IMPORTANT
Sudden cardiac death – Primary prevention; fibrate versus placebo[93,152]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	3/2051 (0.15%)	3/2030 (0.15%)	RR 0.99 (0.2 to 4.9)	0 fewer per 1000 (from 1 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT
Sudden cardiac death – Mixed primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	serious[j]	none	70/4895 (1.4%)	54/4900 (1.1%)	RR 1.3 (0.91 to 1.85)	3 more per 1000 (from 1 fewer to 9 more)	⊕⊕OO LOW	IMPORTANT
Sudden cardiac death – Secondary prevention; fibrate versus placebo[87,87]												
1	randomised trials	very serious[k]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/47 (2.1%)	0/45 (0%)	RR 2.88 (0.12 to 68.79)	-	⊕OOO VERY LOW	IMPORTANT
Stroke – Combined [11,30,31,103-105,107,124,131 225-227]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	339/10472 (3.2%)	376/10462 (3.6%)	RR 0.9 (0.78 to 1.04)	4 fewer per 1000 (from 8 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke – Mixed primary and secondary prevention; fibrate + statin versus statin[31,103-105,107]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	51/2765 (1.8%)	48/2753 (1.7%)	RR 1.06 (0.72 to 1.56)	1 more per 1000 (from 5 fewer to 10 more)	⊕⊕OO LOW	CRITICAL

Stroke – Mixed primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	serious[g]	none	158/4895 (3.2%)	175/4900 (3.6%)	RR 0.9 (0.73 to 1.12)	4 fewer per 1000 (from 10 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Stroke – Secondary prevention; fibrate versus placebo[30,225-227]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[g]	none	130/2812 (4.6%)	153/2809 (5.4%)	RR 0.85 (0.68 to 1.07)	8 fewer per 1000 (from 17 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
Raised alanine aminotransferase (more than 3 times the upper limit of normal) - Primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	serious[i]	none	22/4895 (0.45%)	38/4900 (0.78%)	RR 0.58 (0.34 to 0.98)	3 fewer per 1000 (from 0 fewer to 5 fewer)	⊕⊕OO LOW	LESS IMPORTANT
Raised creatine phosphokinase (more than 10 times the upper limit of normal) - Primary and secondary prevention- diabetes; fibrate versus placebo[11,124,131]												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[d]	very serious[b]	none	3/4895 (0.06%)	4/4900 (0.08%)	RR 0.75 (0.17 to 3.35)	0 fewer per 1000 (from 1 fewer to 2 more)	⊕OOO VERY LOW	LESS IMPORTANT
Hospitalisation – Secondary prevention; fibrates versus placebo[225-227]												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[l]	no serious imprecision	none	591/1264 (46.8%)	621/1267 (49%)	RR 0.95 (0.88 to 1.03)	25 fewer per 1000 (from 59 fewer to 15 more)	⊕⊕OO LOW	LESS IMPORTANT

a 2/8 studies unclear allocation concealment, 1/8 studies unclear randomisation, 2/8 studies unclear missing data.
b The lower and upper limits of the confidence interval cross the minimal importance differences (0.75 and 1.25, respectively) making the effect size uncertain.
c 1/2 studies unclear allocation concealment and unclear missing data.
d 94% of subjects in both fibrate and control group started statin therapy during study.
e The upper limit of the confidence interval crosses the minimal important difference (1.25) making the effect size uncertain.
f 1/3 unclear randomisation and allocation concealment, unclear missing data.
g The lower limit of the confidence interval crosses minimal important (0.75) difference making effect size uncertain.
h Unclear randomisation and allocation concealment, unclear missing data.
i The upper limit of the confidence interval crosses the minimal important difference (0.75) making the effect size uncertain.
j The lower limit of the confidence interval crosses the minimal important difference (1.25) making the effect size uncertain.
k Unclear allocation concealment and unclear missing data.
l Hospitalisation for unstable angina or chronic heart failure only.

12.4 Economic evidence

Published literature

One economic evaluation was included that compared fibrates with placebo in adults with established CVD.[200] This is summarised in the economic evidence profile below (Table 86) and the economic evidence tables in Appendix H.

No relevant economic evaluations were identified that compared fibrates with either placebo or statins in adults without established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease.

Two economic evaluations in adults with type 2 diabetes relating to this review question were identified but were excluded due to limited applicability of the evidence.[45,90] These are listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 86: Economic evidence profile: fibrates versus placebo for secondary prevention of CVD

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Nyman 2002[200] (USA)	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Gemfibrozil, 1.2 g/day • Study population: men with low HDL cholesterol and low LDL cholesterol • Probabilistic decision analytic model based on outcomes and costs of VA-HIT[225-227] • Lifetime horizon based on treatment for 5 years • Cost year: 1998 (US) [(c)]	£2379	0.32 QALYs gained	ICER: £6998 per QALY gained	This base case is for a man aged 65 years at start of treatment. The ICER varied from £6325 per QALY gained for patients aged 75 years to £8254 for patients aged 55 years. ICERs were slightly lower (£5708 to £7254 per QALY gained) when a higher utility value (perfect health) was assumed. Probabilistic sensitivity analysis was not undertaken.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

(a) 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 are about half of the wholesale price used in the study and so would tend to reduce the ICERs quoted. 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 sub-population studied, but are not applicable to secondary prevention populations in general.

(b) The model does not consider the effects on cost or health-related quality of life 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.

(c) Converted using 2009 purchasing power parities.[204]

12.5 Evidence statements

Clinical

Combined primary and secondary prevention studies with and without diabetes

- Moderate quality evidence showed that there is no clinical difference between fibrates and placebo or fibrates plus statin and statin at reducing all-cause mortality at up to 6 years [8 studies, n=27,373].
- Moderate quality evidence showed that there is no clinical difference between fibrates and placebo or fibrates plus statin and statin at reducing CV mortality at up to 5 years [3 studies, n=9291].
- Moderate quality evidence suggested that fibrates are potentially more clinically effective when compared to placebo and when fibrates plus statins are compared to statins at reducing non-fatal MI at 6 years [5 studies, n=25,015].
- Low quality evidence suggested that there may be no clinical difference at reducing sudden cardiac death at up to 5 years, but the direction of the estimate of effect could favour either intervention [3 studies n=13,968].
- High quality evidence showed that there is no clinical difference between fibrates and placebo or fibrates plus statin and statin at reducing stroke at up to 6 years [4 studies, n=11,509].

Primary prevention studies

- Low quality evidence suggested that there may be no clinical difference at reducing all-cause mortality at 5 years, but the direction of the estimate of effect could favour either intervention [1 study n=4081].
- Moderate quality evidence suggested that fibrates are potentially more clinically effective when compared to placebo at reducing non-fatal MI at 5 years [1 study n=4081].
- Low quality evidence suggested that there may be no clinical difference at reducing sudden cardiac death at 5 years, but the direction of the estimate of effect could favour either intervention [1 study n=4081].

Mixed primary and secondary prevention population with diabetes studies

- Low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing all-cause mortality at 5 years, but the direction of the estimate of effect favoured placebo [2 studies, n=1023].
- Low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing CV mortality at 5 years, but the direction of the estimate of effect favoured placebo [1 study n=9795].
- Low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing non-fatal MI at 5 years, but the direction of the estimate of effect favoured fibrates [1 study n=9795].
- Low quality evidence suggested that placebo is potentially more clinically effective when compared to fibrates at reducing sudden cardiac death at 5 years, but the direction of the estimate of effect could favour either intervention [1 study n=9795].
- Low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing stroke at 5 years, but the direction of the estimate of effect favoured fibrates [1 study n=9795].

- Low quality evidence suggested that fibrates are potentially more clinically effective when compared to placebo at showing a reduced rate of alanine phosphokinase at 5 years [1 study n=9795].
- Very low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at causing raised creatine kinase at 5 years, but the direction of the estimate of effect favoured fibrates [1 study n=9795].
- High quality evidence showed that there is no clinical difference between fibrates plus statin and statin at reducing all-cause mortality at 5 years [1 study, n=5518].
- Moderate quality evidence suggested that there may be no clinical difference between fibrates plus statin when compared to statin at reducing CV mortality at 5 years, but the direction of the estimate of effect favoured fibrates [1 study, n=5518].
- High quality evidence showed that there is no clinical difference between fibrates plus statin and statins at non-fatal MI at 5 years [1 study, n=5518].
- Low quality evidence suggested that there may be no clinical difference between fibrates plus statin and statin at reducing stroke at up to 5 years, but the direction of the estimate of effect could favour either intervention [1 study, n=5518].

Secondary prevention studies

- High quality evidence showed that there is no clinical difference between fibrates and placebo at reducing all-cause mortality at up to 6 years [4 studies, n=7561].
- Very low quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing CV mortality at 5 years, but the direction of the estimate of effect favoured fibrates [1 study n=1568].
- Moderate quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing non-fatal MI at 6 years, but the direction of the estimate of effect favoured fibrates [2 studies n=9795].
- Very low quality evidence suggested that placebo is potentially more clinically effective when compared to fibrates at reducing sudden cardiac death at 5 years, but the direction of the estimate of effect could favour either intervention [1 study, n=92].
- Moderate quality evidence suggested that there may be no clinical difference between fibrates when compared to placebo at reducing stroke at 6 years, but the direction of the estimate of effect favoured fibrates [2 studies n=5621].

Economic

- One cost–utility analysis found that in adults with established CVD fibrates were cost effective compared to placebo for the secondary prevention of CVD (ICER: £6996 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

12.6 Recommendations and link to evidence

Recommendation	**90. Do not routinely offer fibrates for the prevention of CVD to any of the following:** • **people who are being treated for primary prevention** • **people who are being treated for secondary prevention** • **people with CKD** • **people with type 1 diabetes** • **people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendations 1.10.2.3 and 1.10.2.4 from Type 2 diabetes (NICE clinical guideline 87) and recommendations 1.10.2.5 and 1.10.2.6 from Type 1 diabetes (NICE clinical guideline 15).]**
Relative values of different outcomes	All-cause mortality, CV mortality, MI, stroke or TIA, and quality of life were considered critical outcomes. Sudden cardiac death was considered an important outcome. Hospitalisation and adverse events and were considered relevant outcomes.
Trade-off between clinical benefits and harms	The evidence suggested that fibrates versus placebo potentially reduce non-fatal MI in primary prevention, secondary prevention and people with type 2 diabetes in primary and secondary prevention. There was no evidence of benefit for all other outcomes. The only study that compared fibrates plus statin versus statin found no evidence of benefit for the addition of fibrates for any of the outcomes including non-fatal MI. No evidence of harm was found. No evidence was found for CVD reduction for people with type 1 diabetes and CKD.
Economic consideration	Only 1 economic evaluation was identified.[200,200] This found gemfibrozil to be cost effective compared to placebo for secondary prevention in men with low HDL cholesterol and low LDL cholesterol, based on the VA-HIT study.[225-227] The population was US army veterans, and the study was conducted in 1998, without the use of statins as an alternative or additional treatment. It is not clear if this study is relevant to any sections of the current UK population. The clinical results it used contrast with the overall findings of our clinical review, which found fibrates to have very limited clinical effectiveness for secondary prevention populations as a whole (rather than the unusual subgroup with low HDL cholesterol and low LDL cholesterol). No relevant economic evidence was identified relating to the use of fibrates in a general secondary population, or for primary prevention, or in people with diabetes or CKD. If fibrates are not clinically effective, or have very limited effectiveness, then the use of fibrates is unlikely to be cost effective compared to placebo. Given that the cost of fibrate treatment is substantially greater than that of statin treatment, but that statins have greater effectiveness, fibrate treatment could not be cost effective compared to statin treatment. If the rate of adverse events is higher with fibrates than with statins, as appears to be the case, the costs incurred in dealing with these side effects would favour statins still further. Since no clinical benefit has been found for fibrates with statins compared to statins alone, there is no reason to believe that fibrates with statins could be cost effective compared to statins.
Quality of evidence	Evidence for the use of fibrates in the analyses of all studies combined was of high quality for stroke, moderate quality for the outcomes of all-cause mortality, CV mortality and non-fatal MI and of low or very low for the other outcomes. The evidence for fibrates in primary prevention was all of low quality and from only 1 trial. Quality of evidence for the 3 studies in people with diabetes varied from high to very low. Evidence from 1 of these studies which compared fibrate plus statin versus

	statin was high for the outcomes of all-cause mortality and non-fatal MI, and moderate for the outcome of CV mortality. Evidence for the outcome of hospitalisation from only 1 study in secondary prevention was low.
Other considerations	The GDG were aware of common side effects when fibrates are taken, but also and that a number of patients may not tolerate statins. The GDG noted that the secondary prevention studies were conducted with fibrates in a range of populations including post-MI, prior CABG and PAD. The GDG noted that no studies were found for fibrates in patients with CKD or with type 1 diabetes. The GDG noted that fibrates increase creatinine levels but reduce urine albumin levels. The long-term clinical significance of these actions of fibrates is unclear. The GDG considered that recommendations for fibrates were being made in the context of extensive evidence for the benefit of statins for primary and secondary prevention and that in this context the limited evidence for benefits from fibrate trials did not support their widespread use. The GDG decided that fibrate monotherapy should not be offered routinely. The evidence from combination of fibrate with statin found no benefit from addition of fibrate. Therefore the GDG considered fibrates in combination with statins should not be recommended. The GDG recognised that fibrates are not generally used for primary or secondary prevention in the UK. The GDG noted that fibrates are used clinically in the treatment of patients with severe hypertriglyceridaemia based on subgroups from the fibrate trials, though the evidence base for CVD outcomes for this indication was poor.

12.7 Research recommendation

7. What is the effectiveness of fibrate therapy in patients with mixed hyperlipidaemia?

Why this is important

The prevalence of obesity and of the metabolic syndrome (associated with hypertriglyceridaemia) are increasing in the UK. Statin trials have only recruited people within a narrow range of triglyceride levels (usually less than 4.5 mmol/litre). Post hoc and some pre-specified subgroup analyses of the current trial evidence suggests a potential role for fibrates in people with high triglyceride levels (more than 5 mmol/litre) and low HDL-cholesterol levels, even if treated with a statin.

13 Nicotinic acid for the prevention of CVD

13.1 Introduction

Nicotinic acid (niacin) is also known as vitamin B3. Small doses have been found to prevent deficiency in man and to cure the symptoms that constitute pellagra. It was discovered to reduce cholesterol and atherosclerosis in rabbits in 1954. These findings for high doses of nicotinic acid were extended to people when nicotinic acid was found in 1955 to reduce plasma cholesterol and in 1959 to be effective in the treatment of familial hypercholesterolaemia. Since those early studies nicotinic acid has been described in numerous studies to reduce total cholesterol, LDL cholesterol, triglycerides and lipoprotein(a) and to raise HDL cholesterol. Nicotinic acid is not currently commonly used for people at risk of CVD.

13.2 Review question: What is the clinical and cost effectiveness of nicotinic acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

For full details see review protocol in Appendix C.

Table 87: PICO characteristics of review question

Population	Adults (18 years and over) without established CVD and: • At risk of CVD • Type 1 diabetes • Type 2 diabetes • Chronic kidney disease Adults (18 years and over) with established CVD including: • Prior myocardial infarction • Acute coronary syndromes (STEMI, NSTEMI or unstable angina) • Stable angina • Stroke • Peripheral artery disease
Interventions	• Nicotinic acid versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Nicotinic acid plus statins versus placebo plus statins • Nicotinic acid (no statin) versus placebo (no statin)
Comparisons	Statin or placebo
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • Myocardial infarction • Stroke or transient ischaemic attack (TIA) • Hospitalisation • Adverse events • Quality of life
Study design	RCT, SRs of RCTs

13.3 Clinical evidence

Four studies in secondary prevention were included in the review.[3,14,123,162,231,257] One study compared nicotinic acid versus placebo.[3] Two studies compared nicotinic acid and statin versus placebo and statin.[123,162,257] One study compared nicotinic acid plus laropiprant and statin versus placebo plus statin.[14] Table 88 summarises the studies. Evidence from these are summarised in the clinical GRADE evidence profiles below (Table 89). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

No studies were identified for people at risk of CVD, type 1 diabetes, type 2 diabetes, or CKD.

No studies were identified that reported separate information on black and minority ethnic groups or women or people with a family history of CVD , autoimmune disease, serious mental illness or people in low socioeconomic groups.

Table 88: Summary of studies included in the review

Study	Intervention, comparison	Population	Follow-up	Outcomes	Comments
AIM-HIGH 2011[123,162]	Nicotinic acid plus statin versus placebo plus statin	n=3414 men and women USA	Mean 3 years	All-cause mortality Non-fatal MI Stroke Hospitalisation GI symptoms (for discontinuation of drug only) Flushing (for discontinuation of drug only) Abnormal liver test (for discontinuation of drug only) Elevated glucose levels (for discontinuation of drug only)	Secondary prevention; population included people CAD, cerebro-vascular disease or carotid disease, PAD all with low levels of HDL-C Following randomisation, study investigators were allowed to increase statin dose or to prescribe ezetimibe to patients not achieving a target LDL-cholesterol level (ezetimibe; placebo group 22%, intervention group 10%) Study halted early on the basis of futility
Anon 1975[3,2,31] CDP	Nicotinic acid versus placebo	n=3908 men Multiple countries	Mean 74 months (5 years for GI symptoms, flushing, itching of skin)	All-cause mortality CV mortality Non-fatal MI Sudden cardiac death Stroke Hospitalisation GI symptoms Flushing	Secondary prevention; post-MI

Study	Intervention, comparison	Population	Follow-up	Outcomes	Comments
				Itching of skin	
Anon 2013[14] HPS2-THRIVE	ER niacin/ laropiprant plus statin versus statin	n= 25,673 men and women USA	Median 3.9 years	Non-fatal MI Stroke Rhabdomyolysis Any myopathy Alanine transaminase more than 3 times upper limit of normal GI symptoms (for discontinuation of drug only) Flushing (for discontinuation of drug only)	Secondary prevention; population included people with prior MI, ischaemic stroke, TIA, carotid revascularisation, PAD, diabetes plus CAD or CVD
Taylor 2004[257,257] ARBITER 2	Nicotinic acid plus statin versus placebo plus statin	n=167 men and women USA	12 months	All-cause mortality Stroke	Secondary prevention; population included people with CVD all with low levels of HDL cholesterol

Table 89: Clinical evidence profile: nicotinic acid versus placebo and nicotinic acid plus statin versus statin for secondary prevention of CVD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotinic acid or nicotinic acid plus statin	Placebo or statin	Relative (95% CI)	Absolute		
All-cause mortality - Combined nicotinic acid studies[123,123,162,162,257]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	334/2924 (11.4%)	667/4565 (14.6%)	RR 1.04 (0.92 to 1.17)	6 more per 1000 (from 12 fewer to 25 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	237/1119 (21.2%)	583/2789 (20.9%)	RR 1.01 (0.89 to 1.16)	2 more per 1000 (from 23 fewer to 33 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Nicotinic acid + statin versus statin[123,162,257]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	97/1805 (5.4%)	84/1776 (4.7%)	RR 1.14 (0.86 to 1.51)	7 more per 1000 (from 7 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
CV mortality - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	210/1119 (18.8%)	528/2789 (18.9%)	RR 0.99 (0.86 to 1.14)	2 fewer per 1000 (from 27 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI- Combined nicotinic acid studies[14,123,123,162,162]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	606/15675 (3.9%)	863/17320 (5%)	RR 0.9 (0.81 to 1)	5 fewer per 1000 (from 9 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal MI - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	none	100/1119 (8.9%)	339/2789 (12.2%)	RR 0.74 (0.59 to	32 fewer per 1000 (from 11 fewer to	⊕⊕⊕O MODERATE	CRITICAL

									0.91)	50 fewer)		
Non-fatal MI - Nicotinic acid + statin versus statin[14,123,162]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	506/14556 (3.5%)	524/14531 (3.6%)	RR 0.96 (0.85 to 1.09)	1 fewer per 1000 (from 5 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
Sudden cardiac death - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	118/1119 (10.5%)	269/2789 (9.6%)	RR 1.09 (0.89 to 1.34)	9 more per 1000 (from 11 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Combined nicotinic acid studies[14,123,123,162,162,257]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	613/15762 (3.9%)	789/17400 (4.5%)	RR 0.96 (0.87 to 1.07)	2 fewer per 1000 (from 6 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Stroke - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[d]	none	86/1119 (7.7%)	271/2789 (9.7%)	RR 0.79 (0.63 to 1)	20 fewer per 1000 (from 36 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Nicotinic acid + statin versus statin[14,123,162 257,257]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	527/14643 (3.6%)	518/14611 (3.5%)	RR 1.02 (0.9 to 1.14)	1 more per 1000 (from 4 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
Hospitalisation - Combined nicotinic acid studies[3,123,162,231]												
2	randomised trials	serious[a]	no serious inconsistency	serious[e]	serious[d]	none	378/2791 (13.5%)	1030/4390 (23.5%)	RR 0.82 (0.74 to 0.91)	42 fewer per 1000 (from 21 fewer to 61 fewer)	⊕OOO VERY LOW	LESS IMPORTANT
Hospitalisation - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[d]	none	306/1073 (28.5%)	948/2694 (35.2%)	RR 0.81 (0.73 to 0.9)	67 fewer per 1000 (from 35 fewer to 95 fewer)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Hospitalisation - Nicotinic acid + statin versus statin[123,162]												

1	randomised trials	very serious[a]	no serious inconsistency	very serious[f]	serious[d]	none	72/1718 (4.2%)	82/1696 (4.8%)	RR 0.87 (0.64 to 1.18)	6 fewer per 1000 (from 17 fewer to 9 more)	⊕OOO VERY LOW	LESS IMPORTANT
GI symptoms - Combined nicotinic acid studies[14,123,123,162,162]												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[g]	no serious imprecision	none	751/15629 (4.8%)	616/17225 (3.6%)	RR 1.89 (1.69 to 2.1)	32 more per 1000 (from 25 more to 39 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
GI symptoms - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[h]	no serious imprecision	none	230/1073 (21.4%)	385/2694 (14.3%)	RR 1.5 (1.29 to 1.74)	71 more per 1000 (from 41 more to 106 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
GI symptoms - Nicotinic acid + statin versus statin[14,123,162]												
2	randomised trials	serious[a]	no serious inconsistency	very serious[h]	no serious imprecision	none	521/14556 (3.6%)	231/14531 (1.6%)	RR 2.25 (1.93 to 2.63)	20 more per 1000 (from 15 more to 26 more)	⊕OOO VERY LOW	LESS IMPORTANT
Flushing - Combined nicotinic acid studies[14,123,123,162,162]												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[g]	no serious imprecision	none	1197/15629 (7.7%)	172/17225 (1%)	RR 13.2 (11.46 to 15.21)	122 more per 1000 (from 104 more to 142 more)	⊕⊕⊕O MODERATE	LESS IMPORTANT
Flushing - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	987/1073 (92%)	115/2694 (4.3%)	RR 21.55 (18 to 25.79)	877 more per 1000 (from 726 more to 1000 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Flushing - Nicotinic acid + statin versus statin[14,123,162]												
2	randomised trials	serious[a]	no serious inconsistency	very serious[h]	no serious imprecision	none	210/14556 (1.4%)	57/14531 (0.39%)	RR 3.65 (2.74 to 4.88)	10 more per 1000 (from 7 more to 15 more)	⊕OOO VERY LOW	LESS IMPORTANT
Itching of skin - Nicotinic acid versus placebo[3,231]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	525/1073 (48.9%)	167/2694 (6.2%)	RR 7.89 (6.73 to 9.25)	427 more per 1000 (from 355 more to 511 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

New onset diabetes – Normoglycaemic subjects; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[j]	None	-	-	HR 1.41 (0.97 to 2.04)	-	⊕OOO VERY LOW	LESS IMPORTANT
New onset diabetes - Impaired fasting glucose subject; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[j]	none	-	-	HR 1.34 (1 to 1.8)	-	⊕OOO VERY LOW	LESS IMPORTANT
All-cause mortality - Normoglycaemic patients; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[d]	None	-	-	HR 0.91 (0.74 to 1.12)	-	⊕OOO VERY LOW	CRITICAL
All-cause mortality - Impaired fasting glucose; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[b]	None	-	-	HR 1.19 (0.91 to 1.55)	-	⊕OOO VERY LOW	CRITICAL
All-cause mortality - Type 2 diabetes mellitus; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	very serious[k]	None	-	-	HR 0.99 (0.67 to 1.47)	-	⊕OOO VERY LOW	CRITICAL
Non-fatal MI - Normoglycaemic subjects; nicotinic acid versus placebo[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[d]	None	-	-	HR 0.79 (0.59 to 1.06)	-	⊕OOO VERY LOW	CRITICAL
Non-fatal MI - Impaired fasting glucose[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[c]	none	-	-	HR 0.7 (0.46 to 1.07)	-	⊕OOO VERY LOW	CRITICAL
Non-fatal MI - Type 2 diabetes mellitus[3,231]												
1	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[c]	none	-	-	HR 0.52 (0.26 to	-	⊕OOO VERY LOW	CRITICAL

									1.04)			
Abnormal liver function test - Nicotinic acid + statin versus statin[123,162]												
1	randomised trials	very serious[a]	no serious inconsistency	very serious[h]	very serious[k]	none	5/1718 (0.29%)	5/1696 (0.29%)	RR 0.99 (0.29 to 3.4)	0 fewer per 1000 (from 2 fewer to 7 more)	⊕OOO VERY LOW	LESS IMPORTANT
Increased glucose level - Nicotinic acid + statin versus statin[123,162]												
1	randomised trials	very serious[a]	no serious inconsistency	very serious[h]	serious[j]	none	29/1718 (1.7%)	14/1696 (0.83%)	RR 2.04 (1.08 to 3.86)	9 more per 1000 (from 1 more to 24 more)	⊕OOO VERY LOW	LESS IMPORTANT
Alanine transaminase more than 3 times ULN - Nicotinic acid + statin versus statin[14]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	315/12838 (2.5%)	133/12835 (1%)	RR 2.37 (1.94 to 2.9)	14 more per 1000 (from 10 more to 20 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Rhabdomyolysis - Nicotinic acid + statin versus statin[14,123,162]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/14556 (0.54%)	18/s14531 (0.12%)	RR 4.38 (2.63 to 7.31)	4 more per 1000 (from 2 more to 8 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT
Myopathy - Nicotinic acid + statin versus statin[14]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/12838 (1.2%)	38/12835 (0.3%)	RR 4.08 (2.86 to 5.81)	9 more per 1000 (from 6 more to 14 more)	⊕⊕⊕⊕ HIGH	LESS IMPORTANT

[a] Following randomisation in AIM-HIGH 2011 patients not achieving increase target LDL cholesterol were prescribe ezetimibe or increase in statin; placebo group 22%, intervention group 10%.

[b] The upper limit of the confidence interval crosses the minimal important difference (1.25) making the effect size uncertain.

[c] The upper limit of the confidence interval crosses the minimal important difference (0.75) making the effect size uncertain.

[d] The lower limit of the confidence interval crosses the minimal important difference (0.75) making the effect size uncertain.

[e] 1/2 studies hospitalisation for acute coronary syndrome only.

[f] Hospitalisation for acute coronary syndrome only.

[g] 2/3 studies for discontinuation of study medication.

[h] For discontinuation of study medication only.

[i] Post-hoc analysis.

[j] The lower limit of the confidence interval crosses the minimal important difference (1.25) making the effect size uncertain.

[k] The lower and upper limit of the confidence interval cross the minimal important differences (0.75 and 1.25, respectively) making the effect size uncertain.

13.4 Economic evidence

Published literature

No relevant economic evaluations were identified that compared nicotinic acids with either placebo or statins in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease. See also the economic article selection flow chart in Appendix E.

13.5 Evidence statements

Clinical

Nicotinic acid versus statin in secondary prevention

- High quality evidence showed that there is no clinical difference between nicotinic acid and placebo at reducing all-cause mortality at 74 months [1 study, n=3908].
- High quality evidence showed that there is no clinical difference between nicotinic acid and placebo at reducing CV mortality at 74 months [1 study, n=3908].
- Moderate quality evidence suggested that nicotinic acid is potentially more clinically effective when compared to placebo at reducing non-fatal MI at 74 months [1 study, n=3908].
- Moderate quality evidence suggested that there may be no clinical difference between nicotinic acid when compared to placebo at reducing sudden cardiac death at 74 months, but the direction of the estimate of effect favoured nicotinic acid [1 study, n=3908].
- Moderate quality evidence suggested that there may be no clinical difference between nicotinic acid when compared to placebo at reducing stroke at 74 months, but the direction of the estimate of effect favoured nicotinic acid [1 study, n=3908].
- Moderate quality evidence suggested that there may be no clinical difference between nicotinic acid when compared to placebo at reducing hospitalisation at 74 months, but the direction of the estimate of effect favoured nicotinic acid [1 study, n=3908].
- High quality evidence showed that placebo is more clinically effective when compared to nicotinic acid at showing a reduced rate of GI symptoms at 5 years [1 study, n=3908].
- High quality evidence showed that placebo is more clinically effective when compared to nicotinic acid at showing a reduced rate of flushing at 5 years [1 study, n=3908].
- High quality evidence showed that placebo is more clinically effective when compared to nicotinic acid at showing a reduced rate of itching at 5 years [1 study, n=3908].
- Very low quality evidence suggested that placebo is potentially more clinically effective when compared to nicotinic acid at reducing new-onset diabetes at 74 months in both normoglycaemic and impaired fasting glucose subjects [1 study, n=3908].
- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid when compared to placebo at reducing all-cause mortality at 74 months in normoglycaemic subjects, but the direction of the estimate of effect favoured nicotinic acid [1 study, n=3908].
- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid when compared to placebo at reducing all-cause mortality at 74 months in impaired fasting glucose subjects, but the direction of the estimate of effect favoured placebo [1 study, n=3908].
- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid and placebo at reducing all-cause mortality at 74 months in type 2 diabetics, but the direction of the estimate of effect could favour either intervention [1 study, n=3908].

- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid and placebo at reducing non-fatal MI at 74 months in normoglycaemic subjects, but the direction of the estimate of effect could favour either intervention [1 study, n=3908].
- Very low evidence suggested that nicotinic acid is potentially more clinically effective when compared to placebo at reducing non-fatal MI at 74 months in impaired fasting glucose and diabetic subjects [1 study, n=3908].

Nicotinic acid and statin versus statin in secondary prevention

- Low quality evidence suggested that there may be no clinical difference between nicotinic acid plus statin when compared to statin at reducing all-cause mortality between 1 and 3 years, but the direction of the estimate of effect favoured statin [2 studies, n=3581].
- High quality evidence showed that there is no clinical difference between nicotinic acid plus statin and statin at reducing non-fatal MI between 3 to 3.9 years [2 studies, n=29,087].
- Moderate quality evidence showed that there is no clinical difference between nicotinic acid plus statin and statin at reducing stroke between 1 to 3.9 years [3 studies, n=29,254].
- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid plus statin when compared to statin at reducing hospitalisation at 3 years, but the direction of the estimate of effect favoured nicotinic acid plus statin [1 study, n=3414].
- Very low quality evidence showed that statin is more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of GI adverse events between 3 to 3.9 years [2 studies, n=29,087].
- Very low quality evidence showed that nicotinic acid plus statin is potentially more clinically effective when compared to statin at showing a reduced rate of increased blood sugar level 3 years [1 study, n=3414].
- Very low quality evidence suggested that there may be no clinical difference between nicotinic acid plus statin and statin at showing a reduced rate of abnormal liver function at 3 years, but the direction of the estimate of effect could favour either intervention [1 study, n=3414].
- Very low quality evidence suggested that statin is potentially more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of flushing between 3 to 3.9 years [2 studies, n=29,087].
- High quality evidence showed that statin is more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of increased alanine transaminase levels at 3.9 years [1 study, n=25,673].
- High quality evidence showed that statin is more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of increased alanine transaminase (more than 3 times upper limit of normal) at 3.9 years [1 study, n=25,673].
- High quality evidence showed that statin is more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of rhabdomyolysis at 3.9 years [1 study, n=25,673].
- High quality evidence showed that statin is more clinically effective when compared to nicotinic acid plus statin at showing a reduced rate of myopathy at 3.9 years [1 study, n=25,673].

Economic

- No relevant economic evaluations were identified.

13.6 Recommendations and link to evidence

Recommendation	**91. Do not offer nicotinic acid (niacin) for the prevention of CVD to any of the following:** • **people who are being treated for primary prevention** • **people who are being treated for secondary prevention** • **people with CKD** • **people with type 1 diabetes** • **people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.3.1 from Type 2 diabetes (NICE clinical guideline 87) and recommendation 1.10.2.5 from Type 1 diabetes (NICE clinical guideline 15).]**
Relative values of different outcomes	All-cause mortality, CV mortality, non-fatal MI, stroke or TIA, and quality of life were considered critical outcomes. Sudden cardiac death was considered an important outcome. Hospitalisation and adverse events were considered relevant outcomes.
Trade-off between clinical benefits and harms	The RCT evidence from 1 study in secondary prevention indicated that nicotinic acid monotherapy was potentially more clinically effective when compared to placebo at reducing non-fatal MI and stroke. However, no clinical evidence of reducing non-fatal MI and stroke was found for the intervention of nicotinic acid plus statin versus statin. No RCT evidence of any benefits or harms was found for the mortality outcomes of all-cause mortality, CV mortality and sudden cardiac death for either nicotinic acid monotherapy or nicotinic acid in combination with statin. Post hoc subgroup analysis of the nicotinic acid monotherapy study suggested that there was no benefit or harm for the outcomes of all-cause mortality and non-fatal MI in normoglycaemic patients, impaired glucose fasting patients and type 2 diabetics. New-onset diabetes was potentially increased in normoglycaemic patients and impaired glucose fasting patients taking nicotinic acid. A wide range of adverse events were found in people taking nicotinic acid: GI symptoms, flushing, itching, raised alanine transaminase, abnormal liver function test, rhabdomyolysis and myopathy. These were most marked for flushing, itching, increased alanine transaminase, rhabdomyolysis and myopathy. No evidence was found for the use of nicotinic acid in populations for the primary prevention of CVD, and no trial evidence was found for populations with CKD or type 1 diabetes. No evidence was found for nicotinic acid therapy and outcomes assessing quality of life.
Economic considerations	No relevant economic evidence was identified. The clinical review showed no clear indication of health benefit, and so there is unlikely to be benefit to quality or length of life. There is however clear evidence of increased adverse events, which would decrease quality of life. Using nicotinic acid will incur the cost of the drugs, and the costs of treating any side effects. There is no reason to believe that nicotinic acid will reduce any other healthcare use. With no increase in quality of life and increased costs the use of nicotinic acid could not be cost effective.
Quality of evidence	RCT evidence for the CVD and mortality outcomes was all of high or moderate quality, with the exception of all-cause mortality for the comparison of nicotinic acid plus statin versus statin which was of low quality. The quality of evidence for adverse events outcomes varied from high to very low. The RCT evidence from the combined study analysis of nicotinic acid monotherapy and nicotinic acid plus statin was of moderate quality for GI symptoms and flushing. The outcome of increased GI symptoms for nicotinic acid monotherapy was of moderate quality and of very low quality for the comparison of nicotinic acid plus

	statin versus statin. Evidence for itching was of moderate quality for the combined analysis, and high and very low for nicotinic acid monotherapy and nicotinic acid plus statin respectively. Evidence for raised alanine transaminase, rhabdomyolysis and myopathy was high for the comparison of nicotinic acid plus statin versus statin, while the evidence for abnormal liver function tests and increased glucose levels was of very low quality. The outcome of hospitalisation was of moderate quality in the nicotinic acid monotherapy study and of very low quality in 1 RCT comparing nicotinic acid plus statin versus statin. Evidence from a post hoc subgroup analysis of normoglycaemic and impaired fasting glucose patients and type 2 diabetics examining nicotinic acid monotherapy was of a very low quality for all outcomes; all-cause mortality, non-fatal MI and new onset diabetes.
Other considerations	The GDG were aware of the common occurrence of side effects such as GI side effects and flushing in people who take nicotinic acids. The GDG noted that the adverse event outcomes of GI symptoms and flushing were for study discontinuation in 2 studies comparing nicotinic acid plus statin versus statin (AIM-HIGH 2011[123,162] and HPS2-THRIVE 2013[14]). The GDG discussed the methodological bias in the AIM-HIGH 2011 study: following randomisation, the investigators were allowed to increase statin dose or to prescribe ezetimibe to patients not achieving a target LDL cholesterol. There were a higher number of patients taking ezetimibe in the placebo group (22%) compared with the intervention group (10%). The study was also halted earlier than originally planned on the basis of futility. The GDG also noted that patient blinding was maintained in the AIM-HIGH 2011 study[123,162] by the use of low dose (50–100 mg) nicotinic acid in the 'placebo' treatment arm while 2000 mg was prescribed in the active treatment arm. This may have led to a reduction in the difference between the 2 arms of the study for the incidence of flushing and itching of skin and possibly other categories of adverse events. The GDG noted that the most recent study (HPS2-THRIVE 2013[14]) had considerably more participants (25,673 people) than the other studies included in the evidence review. Considering the common occurrence of side effects and the evidence of limited efficacy in reducing CVD outcomes the GDG considered there was not a role for use of nicotinic acids in the prevention of CVD. Niacin+laropiprant (Tredaptive) was withdrawn in January 2013 following the presentation of the results of the HPS2-THRIVE trial which suggested that the benefits of this combination did not outweigh the risks.

14 Bile acid sequestrants (anion exchange resins) for the prevention of CVD

Bile acid sequestrants (anion exchange resins) were developed as a drug class in the 1970s to reduce LDL cholesterol.[121,122] Their primary action is to bind gut bile acids and thus to reduce entero-hepatic recirculation of bile acids leading indirectly to reductions in intestinal cholesterol absorption and plasma LDL cholesterol. They have complex actions on enterocyte metabolism including reducing plasma glucose but increasing triglycerides.[57,57] They have little effect on HDL cholesterol. Most data exist for the use of cholestyramine and colestipol but recently a new bile acid sequestrant, colesevelam, has become available which has similar efficacy in reducing LDL cholesterol but possibly fewer side effects. Bile acid sequestrants are now little used for treatment for hyperlipidaemia, though a historical evidence base exists for their effects on surrogate and CVD outcomes.

14.1 Review question: What is the clinical and cost effectiveness of bile acid sequestrants (anion exchange resins) versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

For full details see review protocol in Appendix C.

Table 90: PICO characteristics of review question

Population	Adults (18 years and over) without established CVD and: • At risk of CVD • Type 1 diabetes • Type 2 diabetes • Chronic kidney disease Adults (18 years and over) with established CVD including: • Prior myocardial infarction • Acute coronary syndromes (STEMI, NSTEMI or unstable angina) • Stable angina • Stroke • Peripheral artery disease
Interventions	• Bile acid sequestrants (anion exchange resins) versus placebo (then report statin usage as given in RCT baseline characteristics for each arm) • Bile acid sequestrants (plus statins) versus statins • Bile acid sequestrants (no statin) versus placebo (no statin)
Comparisons	Statin or placebo
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • MI • Stroke or transient ischaemic attack (TIA) • Hospitalisation • Adverse events • Quality of life
Study design	RCT, SRs of RCTs

14.2 Clinical evidence

Two studies were included in the review.[4,76] One study was conducted in a primary prevention population.[4]The second study[76,76] considered a combined population for primary and secondary prevention, and reported results for men and women separately. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 92). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J. None of the studies reported results separately for people with type 1 or type 2 diabetes, chronic kidney disease, prior myocardial infarction, acute coronary syndromes (STEMI, NSTEMI or unstable angina), stable angina, stroke or peripheral artery disease.

No studies were identified that reported separate information on black and minority ethnic groups or women or people with a family history of CVD, autoimmune disease, serious mental illness or people in low socioeconomic groups.

Table 91: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Follow up time	Comments
LRC-CPPT 1984[4]	Cholestyramine resin versus placebo USA	n=3806, men	All-cause mortality Myocardial infarction Adverse events Hospitalisation	7.4 years	Primary prevention; men with elevated LDL cholesterol
Dorr 1978[76,76]	Colestipol HCl versus placebo USAs	n=1094, men	All-cause mortality CV mortality Myocardial infarction	3 years	Primary and secondary prevention
		n=1184, women	All-cause mortality		

Table 92: Clinical evidence profile: bile acid sequestrants versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bile acid sequestrants	Placebo	Relative (95% CI)	Absolute		
All-cause mortality - Combined studies[4,76]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	105/3055 (3.4%)	119/3029 (3.9%)	RR 0.88 (0.68 to 1.13)	5 fewer per 1000 (from 13 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality - Primary prevention[4]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	68/1906 (3.6%)	71/1900 (3.7%)	RR 0.95 (0.69 to 1.32)	2 fewer per 1000 (from 12 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality – Primary and secondary prevention (men)[76,76]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	17/548 (3.1%)	27/546 (4.9%)	RR 0.63 (0.35 to 1.14)	18 fewer per 1000 (from 32 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality – Primary and secondary prevention (women)[76,76]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	20/601 (3.3%)	21/583 (3.6%)	RR 0.92 (0.51 to 1.69)	3 fewer per 1000 (from 18 fewer to 25 more)	⊕⊕OO LOW	CRITICAL
CV mortality (overall) – primary and secondary prevention[76,76]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	24/548 (4.4%)	11/546 (2%)	RR 2.17 (1.08 to 4.39)	24 more per 1000 (from 2 more to 68 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction – Combined studies[4,76]												
2	randomised trials	no serious risk of bias	serious[d]	no serious indirectness	serious[a]	none	138/2454 (5.6%)	158/2446 (6.5%)	RR 0.87 (0.7 to 1.08)	8 fewer per 1000 (from 19 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction - Primary prevention[4]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	130/1906 (6.8%)	158/1900 (8.3%)	RR 0.82 (0.66 to 1.03)	15 fewer per 1000 (from 28 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
Myocardial infarction - Combined primary and secondary prevention (men)[76,76]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[c]	none	8/548 (1.5%)	0/546 (0%)	RR 16.94 (0.98 to 292.74)	Not estimable	⊕⊕OO LOW	CRITICAL
Hospitalisation - Primary prevention[4]												
1	randomised	no serious	no serious	serious[e]	no serious	none	287/1906	314/1900	RR 0.91	15 fewer per 1000	⊕⊕⊕O	LESS

	trials	risk of bias	inconsistency		imprecision		(15.1%)	(16.5%)	(0.79 to 1.06)	(from 35 fewer to 10 more)	MODERATE	IMPORTANT
Gastro-intestinal side effect - Primary prevention)[4]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	29/1906 (1.5%)	26/1900 (1.4%)	RR 1.11 (0.66 to 1.88)	2 more per 1000 (from 5 fewer to 12 more)	⊕⊕OO LOW	LESS IMPORTANT
Sudden cardiac death Combined primary and secondary prevention (men)[76,76]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	6/548 (1.1%)	6/546 (1.1%)	RR 1 (0.32 to 3.07)	0 fewer per 1000 (from 7 fewer to 23 more)	⊕⊕OO LOW	LESS IMPORTANT

[a]Point estimate crosses 1 default MID (0.75).
[b]Point estimate crosses 2 default MIDs (0.75 and 1.25).
[c]Point estimate crosses 1 default MID (1.25); wide confidence interval.
[d]I^2 > 75%.
[e]Hospital admissions also due to non CV causes or not side effects of drug.

14.3 Economic evidence

Published literature

No relevant economic evaluations were identified that compared bile acid sequestrants with either placebo or statins in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease. See also the economic article selection flow chart in Appendix E.

14.4 Evidence statements

Clinical: primary prevention of CVD

- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing all-cause mortality, but the direction of the estimate of the effect could favour either intervention (1 study, n=3806 men).
- Moderate quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing myocardial infarction, but the direction of the estimate of the effect favoured bile acid sequestrants (1 study, n=3806 men).
- Moderate quality evidence showed there is no clinical difference between bile acid sequestrants and placebo at reducing hospitalisation (1 study, n=3806 men).
- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at causing GI side adverse events, but the direction of the estimate of the effect could favour either interventions (1 study, n=3806 men).

Clinical: overall – primary and secondary prevention of CVD

- Moderate evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing all-cause mortality, but the direction of the estimate of the effect favoured bile acid sequestrants (1 study, n=2278 men and women).
- Moderate evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing all-cause mortality in men, but the direction of the estimate of the effect favoured bile acid sequestrants (1 study, n=1094 men).
- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing all-cause mortality in women, but the direction of the estimate of the effect could favour either interventions (1 study, n=1184 women).
- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing CV mortality rates, but the direction of the estimate of the effect could favour either interventions (1 study, n=1094 men).
- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing myocardial infarction rates, but the direction of the estimate of the effect could favour either interventions (1 study, n=1094 men).
- Low quality evidence showed there may be no clinical difference between bile acid sequestrants and placebo at reducing sudden cardiac death rates, but the direction of the estimate of the effect could favour either interventions (1 study, n=1094 men).

Economic

No relevant economic evaluations were identified.

14.5 Recommendations and link to evidence

Recommendation	**92. Do not offer a bile acid sequestrant (anion exchange resin) for the prevention of CVD to any of the following:** • **people who are being treated for primary prevention** • **people who are being treated for secondary prevention** • **people with CKD** • **people with type 1 diabetes** • **people with type 2 diabetes. [new 2014] [This recommendation updates and replaces recommendation 1.10.2.5 from Type 1 diabetes (NICE clinical guideline 15).]**
Relative values of different outcomes	All-cause mortality, CV mortality, MI, stroke or TIA, and quality of life were considered the most critical outcomes. Sudden cardiac death was considered to be an important outcome. Hospitalisation and adverse events and were considered to be relevant outcomes.
Trade-off between clinical benefits and harms	For the primary prevention group, the evidence for all-cause mortality, MI, hospitalisation and adverse events did not show any clear indication of either benefit or harms. No data were provided on CV mortality, sudden cardiac death, stroke or quality of life. For the secondary prevention group, the evidence for all-cause mortality, CV mortality, MI, and sudden cardiac death did not show any clear indication of either benefit or harms. However, the evidence found is for a mixed population of primary and secondary prevention, so it is not possible to disentangle evidence for secondary prevention from primary prevention No data were provided on stroke or quality of life. No evidence was found for people with type 1 or 2 diabetes and CKD.
Economic considerations	No relevant economic evidence was identified. The clinical review showed no clear indication of benefit, and so there is unlikely to be benefit to quality or length of life. The drugs do have significant costs, and there is no reason to believe they are likely to reduce other healthcare use. Therefore it is very unlikely that the use of bile acid sequestrants could be cost effective.
Quality of evidence	For the primary prevention group, the data found was of moderate (MI and hospitalisation) or low (all-cause mortality and GI side effects) quality in a men-only population. The LRC-CPPT (1984) study[76,76] was conducted before statins become available, therefore it does not represent current clinical practice. Currently bile acid sequestrants are not prescribed as first line therapy. For the secondary prevention group, the data found was of moderate (all-cause mortality) or low (CV mortality, MI and sudden cardiac death) quality. Data for women were available for all-cause mortality only, the rest of the data were for a men-only population. The LRC-CPPT (1984) study[76] was conducted before statins become available, therefore it does not represent current clinical practice. Currently bile acid sequestrants are not prescribed as first line therapy.
Other considerations	Although the evidence found suggest that bile acid sequestrants are unlikely to cause any benefits or harms, the GDG were aware that these drugs can cause hyper-triglyceridaemia. No outcomes evidence was found for colesevelam, however the GDG noted that this drug is effective in reducing HbA_{1c}. The GDG would also like to highlight that bile acid sequestrants may have a role in reducing LDL cholesterol in other conditions, for example in familial hypercholesterolaemia (NICE clinical guideline 71).[185] Bile acid sequestrants (anion exchange resin) have been considered a treatment option if a patient cannot tolerate a statin. However, the GDG experience is of low adherence to bile acid sequestrants due to their high rate of gastrointestinal side

	effects. The GDG also noted that bile acid sequestrants can cause numerous drug interactions through their effects on the absorption of lipophilic compounds. Given the lack of evidence for efficacy and side effect and interaction profile, the GDG did not consider bile acid sequestrants could be considered as an option for prevention of CVD. Although no evidence was found for people with type 1 or 2 diabetes and CKD, the GDG felt considered it was appropriate to use the evidence for the primary and secondary populations as indirect evidence for those groups and therefore apply the same recommendation of not offering bile acid sequestrant for the prevention of CVD.

15 Omega-3 fatty acid compounds for the prevention of CVD

15.1 Introduction

Omega-3 fatty acid compounds are found in high concentrations in fish and at lower concentrations in plants. Pharmacological preparations of omega-3 fatty acid compounds contain either docosahexaenoic acid (DHA) with eicosapentatenoic acid (EPA,) or EPA alone. Clinically high doses of omega-3 fatty acid compounds have been found to reduce plasma triglycerides in a dose-dependent manner. They have no effect on HDL cholesterol and may raise LDL cholesterol.[273,273]

Omega-3 fatty acid compounds have been considered for the prevention of CVD in people at high risk. Low doses of omega-3 fatty acid compounds have been used for non-lipid-related actions, which are postulated to include reductions in rates of cardiac arrhythmias and plasma concentrations of markers of inflammation. The evidence review considered the effect of omega-3 fatty acid compounds on CV outcomes associated with atherosclerotic disease.

15.2 Review question: What is the clinical and cost effectiveness of omega-3 fatty acids versus placebo or statins for adults without established CVD (primary prevention) and with established CVD (secondary prevention)?

For full details see review protocol in Appendix C.

Table 93: PICO characteristics of review question

Population	Adults (18 years and over) without established CVD and: • At risk of CVD • Type 1 diabetes • Type 2 diabetes • Chronic kidney disease Adults (18 years and over) with established CVD including: • Prior myocardial infarction • Acute coronary syndromes (STEMI, NSTEMI or unstable angina) • Stable angina • Stroke • Peripheral artery disease
Interventions	• 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)
Comparisons	Statin or placebo
Outcomes	• All-cause mortality • CV mortality • Sudden cardiac death • Myocardial infarction • Stroke or TIA (transient ischaemic attack) • Hospitalisation

	• Adverse events • Quality of life
Study design	RCT, SRs of RCTs

15.3 Clinical evidence

Ten studies were included in the review.[34,81,96,149,153,195,218,244,265,287] One study[81,81] considered primary prevention only; it was conducted in healthy men with hypercholesterolaemia. One study[76,287] considered a combined primary and secondary prevention population, and reported results separately. Seven studies[96,149,153,195,218,244,265] were for secondary prevention of CVD. One study[34,34] was conducted in patients with type 2 diabetes. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 95). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J. None of the studies reported results separately for people with type 1 diabetes or chronic kidney disease.

No studies were identified that reported separate information on black and minority ethnic groups or women or people with a family history of CVD, autoimmune disease, serious mental illness or people in low socioeconomic groups.

Table 94: Summary of studies included in the review

Study	Intervention/ comparison	Population	Outcomes	Follow up time	Comments
Einvik 2010[81,81] DOIT	Omega-3 (2.4 g) versus placebo (corn oil capsules. 56% linoleic acid, 32% oleic acid, 10% palmitic acid)	n=563 Norway	All-cause mortality CV mortality	3 years	Primary prevention (men with hyper-cholesterolaemia)
Yokoyama 2007[286,287] JELIS	Omega-3 (EPA 1800 mg/day) + statins (10 mg pravastatin or 5 mg simvastatin) versus statins (10 mg pravastatin or 5mg simvastatin)	n=18,645 (n=14,981 primary prevention; n=3,664 secondary prevention) Japan	All-cause mortality Coronary death Sudden cardiac death Fatal and non-fatal MI Stroke	4.6 years	Overall (80% primary, 20% secondary prevention) Coronary death, sudden cardiac death and MI reported separately for primary and secondary prevention
Galan 2011[95,96] SU.FOL.OM3	Omega-3 (600 mg EPA and DHA at a ratio of 2:1) versus placebo (gelatine capsule)	n=2,501 France	All-cause mortality Non-fatal MI	5 years	Secondary prevention (acute coronary or cerebral ischaemic event within the 12 months of randomisation)
Marchioli 1999[153,153] GISSI	Omega-3 (Omacor: 850–882 mg EPA and DHA at a ratio of 1:2 EPA/DHA, gelatine capsule) versus placebo	n=11,324 Italy	All-cause mortality CV mortality Sudden death Fatal and non-	3.5 years	Secondary prevention (MI within 3 months of randomisation)

Study	Intervention/ comparison	Population	Outcomes	Follow up time	Comments
			fatal stroke		
Nilsen 2001[195,195]	Omega-3 (2 capsules of Omacor, each capsule contains 850–882 mg EPA and DHA 1:2) versus placebo (corn oil)	n=300 Norway	All-cause mortality CV mortality MI	2 years	Secondary prevention (post-MI)
Rauch 2010[218,219] OMEGA	Omega-3 (1 g: 460 mg EPA, 380 mg DHA, soft gelatine capsule) versus placebo (1 g olive oil, soft gelatine capsule)	n=3084 Germany	All-cause mortality Sudden cardiac death	1 year	Secondary prevention (admitted to hospital for acute STEMI or NSTEMI)
Singh 1997 [244,245] IEIS	Omega-3 (1.08 g EPA and 0.72 g DHA) versus placebo (100 mg aluminium hydroxide)	n=240 India	CV mortality Sudden cardiac death Non-fatal MI Adverse events (GI)	1 year	Secondary prevention (post-MI)
von Schacky 1999[265,265] SCIMO	Omega-3 (1 g fish oil) versus placebo	n=223 Germany	Sudden cardiac death Non-fatal MI Adverse events (GI)	2 years	Secondary prevention (proven CAD)
Macchia 2013 [149,149] FORWARD	Omega-3 (1 g fish oil) versus placebo	n=586 Italy and Argentina	All-cause mortality	1 year	Secondary prevention (atrial fibrillation)
Bosch 2012[34,34] ORIGIN	Omega-3 (1 g containing 850 mg EPA and 882 mg DHA) versus placebo	n=12,536 Multicentre	All-cause mortality CV mortality Fatal and non-fatal MI Fatal and non-fatal stroke	6.2 years	Type 2 diabetes

Table 95: Clinical evidence profile: omega-3 fatty acids versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3	Placebo	Relative (95% CI)	Absolute		
All-cause mortality – Combined studies[34,81,96,149,153,195,218,265,287]												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1885/25278 (7.5%)	1945/25230 (7.7%)	RR 0.97 (0.91 to 1.03)	2 fewer per 1000 (from 7 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality - Adults with established CVD[96,149,153,195,218,265]												
6	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	634/9389 (6.8%)	692/9349 (7.4%)	RR 0.91 (0.82 to 1.01)	7 fewer per 1000 (from 13 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality - Adults without established CVD[81,287]												
2	randomised trials	serious[b]	serious[c]	no serious indirectness	no serious imprecision	none	300/9608 (3.1%)	289/9600 (3%)	RR 1.04 (0.88 to 1.22)	1 more per 1000 (from 4 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - Adults with diabetes[34,34]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	951/6281 (15.1%)	964/6281 (15.3%)	RR 0.99 (0.91 to 1.07)	2 fewer per 1000 (from 14 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
CV mortality – Combined studies[34,81,149,244,287]												
s5	randomised trials	serious[d]	serious[e]	no serious indirectness	no serious imprecision	none	914/21677 (4.2%)	998/21657 (4.6%)	RR 0.91 (0.84 to 1)	4 fewer per 1000 (from 7 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
CV mortality - Adults with established CVD[149,244,287]												
3	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	serious[g]	none	323/7611 (4.2%)	395/7617 (5.2%)	RR 0.82 (0.71 to 0.94)	9 fewer per 1000 (from 3 fewer to 15 fewer)	⊕⊕OO LOW	CRITICAL

CV mortality - Adults without established CVD[81,287]												
2	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	very serious[h]	none	17/7785 (0.22%)	22/7759 (0.28%)	RR 0.77 (0.41 to 1.44)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
CV mortality - Adults with diabetes[34,34]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	574/6281 (9.1%)	581/6281 (9.3%)	RR 0.99 (0.89 to 1.1)	1 fewer per 1000 (from 10 fewer to 9 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Myocardial infarction – Combined studies[34,96,195,244,265,287]												
6	randomised trials	no serious risk of bias	serious[i]	no serious indirectness	no serious imprecision	none	485/17244 (2.8%)	485/17201 (2.8%)	RR 1 (0.88 to 1.13)	0 fewer per 1000 (from 3 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
Myocardial infarction - Adults with established CVD[96,195,244,265,287]												
5	randomised trials	serious[j]	no serious inconsistency	no serious indirectness	serious[g]	none	101/3460 (2.9%)	118/3468 (3.4%)	RR 0.85 (0.66 to 1.1)	5 fewer per 1000 (from 12 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction - Adults without established CVD[286,287]												
1	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	serious[g]	none	40/7503 (0.53%)	51/7478 (0.68%)	RR 0.78 (0.52 to 1.18)	2 fewer per 1000 (from 3 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction - Adults with diabetes[34,34]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[l]	none	344/6281 (5.5%)	316/6255 (5.1%)	RR 1.08 (0.93 to 1.26)	4 more per 1000 (from 4 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke – Combined studies[34,96,153,287]												
4	randomised trials	serious[m]	no serious inconsistency	no serious indirectness	no serious imprecision	none	727/22526 (3.2%)	709/22480 (3.2%)	RR 1.02 (0.92 to 1.13)	1 more per 1000 (from 3 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke - Adults with established CVD[96,153]												
2	randomised trials	serious[n]	no serious inconsistency	no serious indirectness	serious[l]	none	127/6919 (1.8%)	108/6906 (1.6%)	RR 1.17 (0.91 to	3 more per 1000 (from 1 fewer to 8	⊕⊕OO LOW	CRITICAL

									1.51)	more)		
Stroke - Adults without established CVD[286,287]												
1	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	serious[l]	none	286/9326 (3.1%)	265/9319 (2.8%)	RR 1.08 (0.91 to 1.27)	2 more per 1000 (from 3 fewer to 8 more)	⊕⊕OO LOW	CRITICAL
Stroke - Adults with diabetes[34,34]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	314/6281 (5%)	336/6255 (5.4%)	RR 0.93 (0.8 to 1.08)	4 fewer per 1000 (from 11 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Gastro-intestinal adverse events - Adults with established CVD[96,244,265]												
3	randomised trials	serious[o]	serious[p]	no serious indirectness	no serious imprecision	none	34/1487 (2.3%)	13/1477 (0.88%)	RR 2.53 (1.35 to 4.73)	13 more per 1000 (from 3 more to 33 more)	⊕⊕OO LOW	LESS IMPORTANT

[a]Marchioli 1999 (GISSI): open-label design.
[b]Einvik 2010 (DOIT) and Yokoyama 2007 (JELIS): high rate of missing data.
[c]Serious heterogeneity (I^2=70%).
[d]Einvik 2010 (DOIT), Yokoyama 2007 (JELIS): high rate of missing data. Marchioli 1999 (GISSI): open-label design.
[e]Serious heterogeneity (I^2=57%).
[f]Yokoyama 2007 (JELIS): high rate of missing data. Marchioli 1999 (GISSI): open-label design.
[g]Confidence interval crosses one default MID (0.75) making the effect size uncertain.
[h]Confidence interval crosses 2 default MIDs (0.75 and 1.25) making the effect size uncertain.
[i]Serious heterogeneity (I^2=50%).
[j]Galan 2011 (SU.FOL.OM3) and Yokoyama 2007 (JELIS): high rate of missing data.
[k]Yokoyama 2007 (JELIS): high rate of missing data.
[l]Confidence interval crosses one default MID (1.25) making the effect size uncertain.
[m]Galan 2011 (SU.FOL.OM3) and Yokoyama 2007 (JELIS): high rate of missing data. Marchioli 1999 (GISSI): open label design.
[n]Galan 2011 (SU.FOL.OM3): high rate of missing data. Marchioli 1999 (GISSI): open-label design.
[o]Galan 2011 (SU.FOL.OM3): high rate of missing data.
[p]Serious heterogeneity (I^2=59%).

15.4 Economic evidence

Published literature

No relevant economic evaluations were identified that compared the use of omega-3 fatty acids with placebo in adults without established CVD, with established CVD, with type 1 diabetes, with type 2 diabetes or with chronic kidney disease.

Five studies of omega-3 fatty acids in adults with established CVD relating to this review were selectively excluded due to methodological limitations.[92,139,174,213,233] These are listed in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

15.5 Evidence statements

Clinical

Primary prevention of CVD

- Low quality evidence showed there is no clinical difference in effect between omega-3 fatty acids and placebo at reducing all-cause mortality [2 studies, n=19,208].
- Very low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing CV mortality, but the direction of the estimate of effect could favour either interventions [2 studies, n=15,544].
- Low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing MI, but the direction of the estimate of effect could favoured omega-3 fatty acids[1 study, n=14,981].
- Low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing stroke, but the direction of the estimate of effect could favoured placebo [1 study, n=18,645].

People with type 2 diabetes

- High quality evidence showed there is no clinical difference in effect between omega-3 fatty acids and placebo at reducing all-cause mortality [1 study, n=13,136].
- High quality evidence showed there is no clinical difference in effect between omega-3 fatty acids and placebo at reducing CV mortality [1 study, n=13,136].
- Moderate quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing MI, but the direction of the estimate of effect could favoured omega-3 fatty acids [1 study, n=13,136].
- High quality evidence showed there is no clinical difference in effect between omega-3 fatty acids and placebo at reducing stroke [1 study, n=13,136].

Secondary prevention of CVD

- Moderate quality evidence showed there is no clinical difference in effect between omega-3 fatty acids and placebo for reducing all-cause mortality [6 studies, n=18,738].
- Low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing CV mortality, but the direction of the estimate of effect could favoured omega-3 fatty acids [3 studies, n=15,228]

- Low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing MI, but the direction of the estimate of effect could favoured omega-3 fatty acids[5 studies, n=6928].
- Low quality evidence showed there may be no clinical difference between omega-3 fatty acids and placebo at reducing stroke, but the direction of the estimate of effect could favoured placebo [2 studies, n=13,825]
- Low quality evidence showed omega-3 fatty acids cased increased rates of GI symptoms compared with placebo at [3 studies, n=2964].

Economic

- No relevant economic evaluations were identified.

15.6 Recommendations and link to evidence

Recommendations in this section update and replace recommendations 1.10.4.1 and 1.10.4.2 from Type 2 diabetes (NICE clinical guideline 87) and recommendation 1.10.2.5 from Type 1 diabetes (NICE clinical guideline 15).

Recommendations	**93. Do not offer omega-3 fatty acid compounds for the prevention of CVD to any of the following:** • **people who are being treated for primary prevention** • **people who are being treated for secondary prevention** • **people with CKD** • **people with type 1 diabetes** • **people with type 2 diabetes. [new 2014]** **94. Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. [new 2014]** **95. Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. [new 2014]**
Relative values of different outcomes	All-cause mortality, CV mortality, MI, stroke or TIA, and quality of life were considered critical outcomes.
Trade-off between clinical benefits and harms	**Primary prevention** In the primary prevention population, there is no evidence of clinical benefits. Adverse effects were not reported in the studies of omega-3 in primary prevention populations; however, there is evidence of increased GI adverse effects for the secondary prevention population, and the GDG considered this as indirect evidence for adverse events in primary prevention. **Secondary prevention** For the secondary prevention of CV disease, the evidence showed that there was no clinical benefit in using preparations of omega-3 fatty acids compounds. In addition, there was evidence of increased GI adverse effects. **Type 2 diabetes** In people with type 2 diabetes, there is no evidence of clinical benefits in taking omega-3 fatty acids compounds to prevent CV disease. Adverse effects were not reported in the study for this population; however, there is evidence of increased GI adverse effect for the secondary prevention population, and the GDG considered this as indirect evidence for people with type 2 diabetes.

	Type 1 diabetes and CKD No outcome trials of omega-3 fatty acids compounds were found in people with type 1 diabetes or CKD.
Economic considerations	No relevant economic evidence was identified. The clinical review found no evidence of health benefit, and so there is unlikely to be any benefit to quality or length of life. The drugs do have significant costs, and there is no reason to believe they are likely to reduce other healthcare use. With no increase in quality of life and increased costs the use of omega-3 fatty acids could not be cost effective. In addition to prescriptions, omega-3 fatty acids are available and commonly purchased over the counter, at cost to the individual. Without evidence of clinical benefit this would not be a prudent use of individuals' money, and so clinicians should advise against the purchasing of such supplements on the grounds of preventing CVD.
Quality of evidence	Overall, the majority of the evidence was of low quality for all outcomes in both the primary and secondary prevention studies. Evidence from was of high or moderate quality for the 1 study conducted exclusively in a type 2 diabetes population. The GDG were made aware that concerns have been raised[275] concerning the implausibility of and possible fraud in the IEIS trial (Singh 1997[244,245]). This paper has not been retracted and hence it is still included in the review, however the results were considered with caution. See also the further comments regarding papers by this author in Chapter X on dietary intervention strategies.
Other considerations	Omega-3 fatty acid compounds are common supplements that can be bought over the counter in most pharmacies, supermarkets and food supplements stores. The GDG felt it was important to advise people at risk of CVD that the use of such supplements is not supported by clinical evidence. This recommendation also reflects the recommendation made in the type 2 diabetes guideline, CG87 (2008).[189] The GDG considered that the effect of omega-3 fatty acids was not different in the different population subgroups, therefore the same recommendation was made against their use for primary and secondary prevention of CVD. Although no evidence was found for people with type 1 diabetes or CKD, the GDG felt it was appropriate to use the evidence from primary, secondary populations and type 2 diabetes populations as indirect evidence and therefore apply the same recommendation of not offering omega-3 fatty acids for people with type 1 diabetes and CKD. The GDG were aware of a published post-hoc analysis[153,154] of the GISSI 1999 study[153,153] that showed most of the clinical benefit of omega-3 fatty acids compounds occurred within 3 months of MI. The GDG noted that the JELIS 2007 study[286,287] is composed entirely of a Japanese population, which is considered to have a significantly different diet from the UK population. **Combination therapy** The GDG considered that there was insufficient evidence to recommend combining a statin with a fibrate, anion exchange resin, omega-3 compounds, or nicotinic acid.

16 Ezetimibe [2008]

16.1 Ezetimibe (for primary prevention)

16.1.1 Evidence statements for ezetimibe

Please refer to NICE Technology Appraisal No. 132 'Ezetimibe for the treatment of primary (heterozygous familial and non familial) hypercholesterolaemia', [183]

16.1.2 Clinical effectiveness of ezetimibe

The NICE Technology Appraisal 132 is entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia', [183]. The guidance recommends ezetimibe as a treatment option for primary (heterozygous familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline.

The population groups covered by the ezetimibe Technology Appraisal 132 (National Institute for Health and Clinical Excellence., 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;
- whose condition is not appropriately controlled with a statin alone or;
- in whom a statin is considered inappropriate or is not tolerated.

The term "not appropriately controlled with a statin alone" is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised and tolerated.

The NICE Technology Appraisal 132 [183] 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n=3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n=2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/l to 6.5 mmol/l and included mixed populations of people with and without a history of CVD.

16.1.3 Cost effectiveness of ezetimibe

Please refer to the cost effectiveness analysis carried out by the NICE Technology Appraisal 132 [183].

2008

16.1.4 Evidence to recommendations - ezetimibe

Please refer to recommendations of the NICE Technology Appraisal 132 entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia'.

16.2 Ezetimibe (for secondary prevention)

16.2.1 Evidence statements for ezetimibe

Please refer to NICE Technology Appraisal No. TA132 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia'.[183]

16.2.2 Clinical effectiveness of ezetimibe

The NICE Technology Appraisal TA132 is entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia'.[183] The guidance recommends ezetimibe as a treatment option for primary (heterozygous familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline (this guidance).

The population groups covered by the ezetimibe Technology Appraisal TA132[183] are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;
- whose condition is not appropriately controlled with a statin alone or;
- in whom a statin is considered inappropriate or is not tolerated.

2008

The term "not appropriately controlled with a statin alone" is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised.

The NICE Technology Appraisal TA132[183] 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia' did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n=3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n=2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD.

16.2.3 Cost-effectiveness of ezetimibe

Please refer to results of the cost-effectiveness analysis carried out by the NICE Technology Appraisal 132.[183]

16.2.4 Evidence into recommendations

Please refer to the NICE Technology Appraisal 132 entitled 'Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia'.

16.2.5 Recommendation

Recommendation	**96. People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal guidance 132). [2008][183]**

2008

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18 Acronyms and abbreviations

ABI	Ankle Brachial Index
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DBP	Diastolic blood pressure
FH	Familial hypercholesterolaemia
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	High-density lipoprotein
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IPD	Individual patient data
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LLT	Lipid-lowering therapy
MA	Meta-analysis
MI	Myocardial infarction
NCGC	National Clinical Guideline Centre
NICE	National Institute for Health and Care Excellence
NA	Not applicable
NNH	Number needed to harm
NNT	Number needed to treat
NR	Not reported
OR	Odds ratio
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SPC	Summary of product characteristics
SR	Systematic review
T1D	Type 1 diabetes

T2D	Type 2 diabetes
TIA	Transient ischaemic attack
ULN	Upper limit of normal
WBC	White blood cells

19 Glossary

Please see also the NICE glossary at: http://www.nice.org.uk/website/glossary/

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.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute coronary syndrome	Acute coronary syndrome refers to a spectrum of acute myocardial ischaemic states from unstable angina to trans-mural myocardial infarction
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
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.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.

	A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers/doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Cardiovascular disease	In this document CVD refers to the combined outcome fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, transient ischaemic attack, angina and acute coronary syndrome.
Cardiovascular event	Fatal or non-fatal myocardial infarct; acute coronary syndrome; fatal or non-fatal stroke; transient ischaemic attack
Cardiovascular risk	The risk of a CV event occurring
Cardiovascular risk assessment	Involves the use of predictive equations and the adjustment of CV 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.
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.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane

	Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis	Cost-consequence analysis is one of the tools used to carry out an economic

(CCA)	evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
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.
Cost–utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
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.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits - health effects - relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the

effect, effect size)	outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.

Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See ‘Product licence’.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Median	The value at the halfway mark when data are ranked in order.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.

Myocardial infarction	Event that results in necrosis of heart muscle.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: number of true negatives / (number of true negatives + number of false negatives)
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups - in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there

	is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Poly-pharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: number of true positives / (number of true positives + number of false positives)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
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 CVD. 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).
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.

Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.

Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed in advance as being less important than the primary outcomes.
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 CVD.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for: If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows the capacity to explore the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. 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).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.

Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).