ClinicalEvidence

Primary prevention of CVD: treating dyslipidaemia

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ABSTRACT

INTRODUCTION: The incidence of dyslipidaemia is high: in 2000, approximately 25% of adults in the USA had total cholesterol greater than 6.2 mmol/L or were taking lipid-lowering medication. Primary prevention in this context is defined as long-term management of people at increased risk but with no clinically overt evidence of CVD — such as acute MI, angina, stroke, and PVD — and who have not undergone revascularisation. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of pharmacological cholesterol-lowering interventions in people at low risk (less than 0.6% annual CHD risk); at medium risk (0.6–1.4% annual CHD risk); and at high risk (at least 1.5% annual CHD risk)? What are the effects of reduced or modified fat diet? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 16 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: ezetimibe, fibrates, niacin (nicotinic acid), reduced- or modified-fat diet, resins, and statins.

QUESTIONS

INTERVENTIONS

Key points

- Dyslipidaemia, defined as elevated total or low-density lipoprotein (LDL) cholesterol levels, or low levels of high-density lipoprotein (HDL) cholesterol, is an important risk factor for coronary heart disease (CHD) and stroke.

  The incidence of dyslipidaemia is high: in 2000, approximately 25% of adults in the US had total cholesterol greater than 6.2 mmol/L, or were taking lipid-lowering medication.

There is a continuous, graded relationship between the total plasma cholesterol concentration and ischaemic heart disease (IHD) morbidity and mortality. IHD is the leading single cause of death in high-income countries and the second in low- and middle-income countries.

Primary prevention in this context is defined as long-term management of people at increased risk, but with no clinically overt evidence of CVD, such as MI, angina, stroke, and peripheral vascular disease, and who have not undergone revascularisation.

- Statins have been shown to be highly effective, particularly in treating people at high risk of CHD (at least 1.5% annual risk of CHD). Although effective in people in all risk categories (low risk, medium risk), it seems that the magnitude of benefit is related to the individual's baseline risk of CHD events.
- In people at medium risk of CHD (0.6–1.4% annual risk of CHD), fibrates have been shown to reduce the rate of CHD, but not of overall mortality, compared with placebo.

  We don't know whether resins are beneficial in reducing non-fatal MI and CHD death in people at medium risk of CHD. We found no evidence relating to the effects of niacin (nicotinic acid) in people at medium risk of CHD.

  We found no evidence that examined the efficacy of niacin, fibrates, or resins in people either at low or high risk of CHD.

  We found no evidence on the effects of ezetimibe in people at low, medium, or high risk of CHD events.
- A reduced- or modified-fat diet may be beneficial in reducing cardiovascular events in people at risk of CHD events.

Clinical context

DEFINITION

Dyslipidaemia, defined as elevated total or low-density lipoprotein (LDL) cholesterol levels, or low levels of high-density lipoprotein (HDL) cholesterol, is an important risk factor for CHD and stroke (cerebrovascular disease). This review examines the evidence for treatment of dyslipidaemia for primary prevention of CHD. Primary prevention in this context is defined as long-term management of people at increased risk, but with no clinically overt evidence of CVD, such as acute MI, angina, stroke, and PVD, and who have not undergone revascularisation. Most adults at increased risk of CVD have no symptoms or obvious signs, but they may be identified by assessment of their risk factors (see aetiology/risk factors below). We have divided people with no known CVD into 3 groups: low risk (<0.6% annual CHD risk), medium risk (0.6–1.4% annual CHD risk), and high risk (1.5% or more annual CHD risk). Prevention of cerebrovascular events is discussed in detail elsewhere in *Clinical Evidence* (see review on stroke prevention). In the US, the preferred method to calculate CVD risk would be to use the Framingham risk equations, the best validated method from a US population. [1]

INCIDENCE/ PREVALENCE

Dyslipidaemia, defined as elevated total or LDL cholesterol, or low HDL cholesterol, is common. Data from the US National Health and Nutrition Examination Survey (NHANES) survey conducted in 1999–2000 found that 25% of adults had total cholesterol >6.2 mmol/L, or were taking a lipid-lowering medication. [2] According to the World Health Report 1999, ischaemic heart disease was the leading single cause of death in the world, the leading single cause of death in high-income countries, and second only to lower respiratory tract infections in low- and middle-income countries. [3] In 1998, it was the leading cause of death, with nearly 7.4 million estimated deaths a year in member states of the WHO, and causing the eighth highest burden of disease in the low- and middle-income countries (30.7 million disability-adjusted life years). [3]

AETIOLOGY/ RISK FACTORS

Major risk factors for ischaemic vascular disease include increased age, male sex, raised LDL cholesterol, reduced HDL cholesterol, raised blood pressure, smoking, diabetes, family history of CVD, obesity, and sedentary lifestyle. For many of these risk factors, including elevated LDL cholesterol, observational studies show a continuous gradient of increasing risk of CVD with increasing levels of the risk factor, with no obvious threshold level. Although, by definition, event rates are higher in high-risk people, most ischaemic vascular events that occur in the population are in people with intermediate levels of absolute risk, because there are many more of them than there are people at high risk. [4]

PROGNOSIS

One Scottish study found that about half of people who have an acute MI die within 28 days, and two-thirds of acute MI occur before the person reaches hospital. [5] People with known CVD are at high risk for future ischaemic heart disease events (see review on secondary prevention of ischaemic cardiac events), as are people with diabetes (see review on diabetes: prevention of cardiovascular events). For people without known CVD, the absolute risk of ischaemic vascular events is generally lower, but varies widely. Estimates of absolute risk can be based on simple risk equations or tables. [6] [7] Such information may be helpful in making treatment decisions.

Primary prevention of CVD: treating dyslipidaemia

AIMS OF INTERVENTION To reduce morbidity and mortality from CHD, with minimum adverse effects.

OUTCOMES Incidence of **CVD events** (fatal and non-fatal ischaemic heart disease events [angina, MI, and sudden cardiac mortality], and stroke), and **mortality**. Where possible, we have reported cardiac mortality and CVD events as separate outcomes. Where studies report composite outcomes (e.g., morbidity and mortality), we have reported the combined data under the heading of CVD events.

METHODS *Clinical Evidence* search December 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2009, Embase 1980 to December 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within the Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded (unless on dietary comparisons), and containing at least 20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all drug comparison studies described as "open", "open label", or not blinded unless blinding was impossible, but included "open" or non-blinded comparison studies on dietary interventions. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of pharmacological cholesterol-lowering interventions in people at low risk (<0.6% annual risk) of CHD?

OPTION EZETIMIBE IN PEOPLE AT LOW RISK — New

We found no direct information from RCTs about the effects of ezetimibe in people at low risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining the effects of ezetimibe in people at low risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION FIBRATES IN PEOPLE AT LOW RISK

We found no direct information from RCTs about the effects of fibrates in people at low risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining the effects of fibrates in people at low risk of CHD events.

Harms: We found no RCTs.

Comment: **Clinical guide:**
The effect of lipid-lowering therapies in people at low risk of CHD events has not been well studied to date.

OPTION NIACIN (NICOTINIC ACID) IN PEOPLE AT LOW RISK

We found no direct information from RCTs about the effects of niacin (nicotinic acid) for lowering cholesterol in people at low risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, **see table, p 15 .**

Benefits: We found no systematic review or RCTs examining the effects of niacin in people at low risk of CHD events.

Harms: We found no RCTs.

Comment: **Clinical guide:**
The effect of lipid-lowering therapies in people at low risk of CHD events has not been well studied to date.

OPTION RESINS IN PEOPLE AT LOW RISK

We found no direct information from RCTs about the effects of resins in people at low risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, **see table, p 15 .**

Benefits: We found no systematic review or RCTs examining the effects of resins in people at low risk of CHD events.

Harms: We found no RCTs.

Comment: **Clinical guide:**
The effect of lipid-lowering therapies in people at low risk of CHD events has not been well studied to date.

OPTION STATINS IN PEOPLE AT LOW RISK

CVD events
Statin plus cholesterol-lowering diet compared with cholesterol-lowering diet alone Adding pravastatin to a cholesterol-reducing diet seems more effective than a cholesterol-lowering diet alone at reducing CHD events (including fatal and non-fatal MI, angina, coronary revascularisation, or cardiac-related sudden death) at 10 years in people with a low risk of CHD (moderate-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, **see table, p 15 .**

Benefits: We found one systematic review (search date 2005, 7 RCTs, 42,848 people) that assessed statins for primary prevention of CVD in people at low, medium, or high risk of CVD (not limited to those with dyslipidaemia). [8] The RCTs included in the review were conducted primarily (90%) in people who did not have apparent CVD. The review identified no RCTs in people with dyslipidaemia and at low risk of CHD. Two RCTs (5749 people) were in people with diabetes, a population that is not within the scope of this review and so these RCTs are not discussed further. One RCT (10,305 people) was in people not deemed to be conventionally dyslipidaemic and so is not discussed further. See Comments section for results of the analysis carried out by the review.

We found one subsequent RCT (7832 hypercholesterolaemic Japanese people with total cholesterol 5.96–6.98 mmol/L, and no history of CHD or stroke) comparing pravastatin 10–20 mg daily plus a cholesterol-lowering diet versus a cholesterol-lowering diet alone. [9] CHD events were defined as fatal and non-fatal MI, angina, coronary revascularisation, or cardiac-related sudden death; the diet assigned was the National Cholesterol Education Program step 1 diet. The RCT found that diet plus pravastatin 10–20 mg daily significantly reduced the rate of CHD over 10 years compared with diet alone (proportion of people with a CHD event: 66/3866 [2%] with diet plus pravastatin *v* 101/3966 [3%] with diet alone; HR 0.67, 95% CI 0.49 to 0.91; P = 0.01). People whose total

cholesterol exceeded 6.98 mmol/L, even after enhancement of assigned treatment regimen, could be given more aggressive treatments, including statins.

A further report of the subsequent RCT [9] analysed data on the rate of CHD in women (5356 women with total cholesterol levels ranging from 5.7 to 7.0 mmol/L). [10] The RCT found no significant difference between pravastatin plus cholesterol-lowering diet and cholesterol-lowering diet alone in rate of CHD events in women at 5 years, although the rate was lower with addition of pravastatin (proportion of women with a CHD event: 26/2638 [0.9%] with diet plus pravastatin *v* 36/2718 [1.3%] with diet alone; HR 0.75, 95% CI 0.45 to 1.25; P = 0.27). The RCT found that the reduction in rate of CHD associated with addition of pravastatin to a cholesterol-lowering diet was greater in older women (aged 60 years or older), but the difference between groups remained non-significant (proportion of women with a CHD event: 16/1380 [1%] with diet plus pravastatin *v* 30/1425 [2%] with diet alone; HR 0.55, 95% CI 0.30 to 1.01; P = 0.054).

Harms: The RCT [9] found no significant difference in the rate of malignant neoplasms or other serious adverse effects between diet alone and diet plus pravastatin (number of all cancers: 119/3866 [3.1%] with diet plus pravastatin *v* 126/3966 [3.2%] with diet alone; HR 0.97, 95% CI 0.97 to 1.25, P = 0.81). The RCT analysing data in only women also found no significant difference between pravastatin plus diet and diet alone in rate of severe adverse effects, including cancers (252/2638 [10%] with diet plus pravastatin *v* 242/2718 [9%] with diet alone; P value not reported; reported as not significant). [10]

Comment: The review found that, compared with placebo, treatment with statins over a mean period of 4.3 years significantly reduced major coronary events, cerebrovascular events, and non-fatal MI (major coronary events: 7 RCTs, 42,848 people; RR 0.71, 95% CI 0.60 to 0.83; cerebrovascular events: RR 0.86, 95% CI 0.75 to 0.97; non-fatal MI: RR 0.68, 95% CI 0.56 to 0.83; absolute numbers not reported). [8] There was no significant difference between statins and placebo in all-cause or CHD mortality (all-cause mortality: RR 0.92, 95% CI 0.84 to 1.01; CHD mortality: RR 0.77, 95% CI 0.56 to 1.08; absolute numbers not reported).

We found one large RCT (17,802 people, median age 66 years) assessing rosuvastatin (20 mg daily) in the primary prevention of cardiovascular events in people with elevated C-reactive protein (2.0 mg/L or more) and levels of LDL below the recommended thresholds for statin treatment. [11] Although the RCT does not cover our population of interest (people with dyslipidaemia), we thought it important to report the RCT as it was terminated early (median follow-up of 1.9 years) because of clear benefit of early treatment with rosuvastatin in the primary prevention of cardiovascular events. Rosuvastatin significantly reduced the composite primary outcome of MI, stroke, arterial revascularisation, hospitalisation for unstable angina, or death from cardiovascular causes compared with placebo (proportion of people with a cardiovascular event: 142/8901 [2%] with rosuvastatin *v* 251/8901 [3%] with placebo; HR 0.56, 95% CI 0.46 to 0.69).

Clinical guide:
The magnitude of the benefit with statin treatment is related to an individual's baseline risk of CHD events, and to the degree of cholesterol lowering, rather than to the initial cholesterol concentration. [8] [12] One systematic review carried out regression analysis of all of the major statin trials (including both primary and secondary prevention settings and a variety of CHD risk levels) and found that mortality benefits of statins outweigh risks in people with a 10-year CHD risk of >13% (see figure 1, p 13). [12]

QUESTION What are the effects of pharmacological cholesterol-lowering interventions in people at medium risk (0.6–1.4% annual risk) of CHD?

OPTION EZETIMIBE IN PEOPLE AT MEDIUM RISK New

We found no direct information from RCTs about ezetimibe for lowering cholesterol in people at medium risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining ezetimibe for lowering cholesterol in people at medium risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION FIBRATES IN PEOPLE AT MEDIUM RISK

Mortality

Compared with placebo Although gemfibrozil is no more effective than placebo at reducing overall mortality in people with a medium risk of CHD, it may be beneficial in people with a higher BMI, higher triglyceride levels, or lower high-density lipoprotein cholesterol levels at baseline (moderate-quality evidence).

CVD events

Compared with placebo Gemfibrozil is more effective than placebo at reducing CHD events at 5 years in people with a medium risk of CHD (high-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

Fibrates versus placebo:

We found no systematic review but found one RCT (4081 middle-aged Finnish men with non-high density lipoprotein cholesterol >200 mg/dL). [13] It found that gemfibrozil 600 mg twice daily significantly reduced CHD events, but not all-cause mortality, over 5 years compared with placebo (CHD events: 56/2051 [3%] with gemfibrozil *v* 84/2030 [4%] with placebo; P <0.02; RR 0.66, 95% CI 0.47 to 0.92; all-cause mortality: 45/2051 [2.2%] with gemfibrozil *v* 42/2030 [2.1%] with placebo; difference reported as not significant; P and CI values not reported). [13] The RCT was followed by an open-label extension for 3.5 years in which 66% of people randomised to gemfibrozil continued to take the drug, and 68% of people randomised to placebo began taking gemfibrozil; at the end of this phase, all participants were offered gemfibrozil for 5 years with no further follow-up to assess compliance. A follow-up study at 18 years assessed all-cause mortality and CHD mortality in the original cohort, using an intention-to-treat analysis. [14] The follow-up study found no significant difference between gemfibrozil and placebo in all-cause mortality or CHD mortality (all-cause mortality per 10,000 person-years: 83% with gemfibrozil *v* 90% with placebo; RR 0.92, 95% CI 0.79 to 1.08; CHD mortality per 10,000 person-years: 27% with gemfibrozil *v* 35% with placebo; RR 0.77, 95% CI 0.59 to 1.00). However, subgroup analyses suggested that participants with higher BMI, higher triglyceride levels, or lower high-density lipoprotein (HDL) cholesterol level at baseline (related to the metabolic syndrome) benefited most from gemfibrozil. For example, in people with a combination of higher BMI (>27.5 kg per m^2) and higher triglyceride levels (184 mg/dL or more), gemfibrozil significantly reduced all-cause mortality and CHD mortality compared with placebo (all-cause mortality per 10,000 person-years: 90% with gemfibrozil *v* 134% with placebo; RR 0.67, 95% CI 0.47 to 0.97; CHD mortality per 10,000 person-years: 21% with gemfibrozil *v* 70% with placebo; RR 0.29, 95% CI 0.15 to 0.97).

Harms:

Fibrates versus placebo:

The RCT found that gemfibrozil significantly increased severe upper-gastrointestinal symptoms in the first year compared with placebo (11.3% with gemfibrozil *v* 7.0% with placebo; P <0.001). [13] It found no significant difference between treatments in constipation, diarrhoea, nausea, or vomiting. The follow-up study gave no information on adverse effects. [14]

Comment:

The subgroup analysis from the RCT supports the use of gemfibrozil in people with high BMI, low HDL cholesterol, and high triglyceride levels. [14]

OPTION NIACIN (NICOTINIC ACID) IN PEOPLE AT MEDIUM RISK

We found no direct information from RCTs about niacin (nicotinic acid) for lowering cholesterol in people at medium risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

We found no systematic review or RCTs examining niacin for lowering cholesterol in people at medium risk of CHD events.

Harms:

We found no RCTs.

Comment:

None.

OPTION RESINS IN PEOPLE AT MEDIUM RISK

CVD events

Compared with placebo Cholestyramine may be more effective at reducing the composite outcome of non-fatal MI and CHD death at 7 years in men aged 35 to 59 years with low-density lipoprotein cholesterol >190 mg/dL; however, results were of borderline significance (low-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

Resins versus placebo:
We found no systematic review but we found one RCT (3806 men aged 35–59 years with low-density lipoprotein cholesterol >190 mg/dL). [15] It found that cholestyramine 24 g daily reduced the combined outcome of non-fatal MI and CHD death compared with placebo at 7.4 years, although the difference did not reach significance as measured using 95% CIs (8% with cholestyramine *v* 10% with placebo; RR 0.81, 90% CI 0.68 to 0.97; P >0.05).

Harms:

Resins versus placebo:
The RCT gave no information on adverse effects. [15]

Comment: None.

OPTION STATINS IN PEOPLE AT MEDIUM RISK

Mortality
Compared with placebo/usual care Statins may be no more effective than placebo or usual care at reducing all-cause or CHD mortality in people with dyslipidaemia (low-quality evidence).

CVD events
Compared with placebo/usual care Statins may be more effective at reducing major coronary events (fatal or non-fatal MI, unstable angina, or sudden cardiac death) at 4.8 to 5.2 years (low-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

Statins versus placebo or usual care:
We found one systematic review (search date 2005, 7 RCTs, 42,848 people) that assessed statins for primary prevention of CVD in people at low, medium, or high risk of CVD (not limited to those with dyslipidaemia). [8] The RCTs included in the review were conducted primarily (90%) in people who did not have apparent CVD. The review did not report results separately for different levels of CHD risk, and so we report results from individual RCTs in people with dyslipidaemia and at moderate risk of CHD (2 RCTs; 16,940 people). [16] [17] Two RCTs (5749 people) were in people with diabetes, a population that is not within the scope of this review and so these RCTs are not discussed further. One RCT (10,305 people) was in people not deemed to be conventionally dyslipidaemic and so is not discussed further. See Comments section of statins in people at low risk of CHD, p 4 for details of the analysis carried out by the review.

The first RCT (5608 men and 997 women with average total and low-density lipoprotein [LDL] cholesterol levels but low level of high-density lipoprotein [HDL] cholesterol) identified by the review compared lovastatin 20 to 40 mg daily versus placebo for 5.2 years. [16] It found that lovastatin significantly reduced major coronary events (defined as fatal or non-fatal MI, unstable angina, or sudden cardiac death) compared with placebo (116/3304 [4%] with lovastatin *v* 183/3301 [6%] with placebo; RR 0.63, 95% CI 0.50 to 0.79). It found no significant difference between treatments in all-cause mortality but the RCT was not powered to detect a difference in this outcome (80/3304 [2.4%] with lovastatin *v* 77/3301 [2.3%] with placebo; difference reported as not significant; P and CI values not reported).

The second RCT (10,355 people with hypertension plus one other risk factor and LDL cholesterol from 120 to 189 mg/dL; about 50% male) identified by the review compared pravastatin 40 mg daily versus usual care. [17] Most people (86%) had no previous history of vascular disease. It found no significant difference between pravastatin and usual care in all-cause mortality or a composite outcome of non-fatal MI or CHD mortality after a mean follow-up of 4.8 years (percentages reported are 6-year incidence rates [absolute numbers not reported]; all-cause mortality: 14.9% with pravastatin *v* 15.3% with usual care; RR 0.99, 95% CI 0.89 to 1.11; non-fatal MI or CHD mortality: 9% with pravastatin *v* 10% with usual care; RR 0.91, 95% CI 0.79 to 1.04). LDL cholesterol was reduced by only 17% after 4 years with pravastatin compared with usual care, in part because 30% of the control group began lipid-lowering drugs during the RCT, which may have contributed to the finding of no significant difference between treatments.

Harms: **Statins versus placebo or usual care:**
The RCT in people at low to medium risk of CHD identified by the review found that a similar proportion of people reported adverse effects with both lovastatin and placebo (14% in each group; absolute numbers not reported; significance not assessed). [16]

The second RCT gave no information on adverse effects. [17]

Comment: **Clinical guide:**
See comments in Statins in people at low risk of CHD, p 4 .

QUESTION What are the effects of pharmacological cholesterol-lowering interventions in people at high risk (1.5% or more annual risk) of CHD?

OPTION EZETIMIBE IN PEOPLE AT HIGH RISK New

We found no direct information from RCTs about ezetimibe for lowering cholesterol in people at high risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining ezetimibe for lowering cholesterol in people at high risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION FIBRATES IN PEOPLE AT HIGH RISK

We found no direct information from RCTs about the effects of fibrates in people at high risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining the effects of fibrates in people at high risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION NIACIN (NICOTINIC ACID) IN PEOPLE AT HIGH RISK

We found no direct information from RCTs about the effects of niacin (nicotinic acid) in people at high risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining the effects of niacin in people at high risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION RESINS IN PEOPLE AT HIGH RISK

We found no direct information from RCTs about the effects of resins in people at high risk of CHD events.

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits: We found no systematic review or RCTs examining the effects of resins in people at high risk of CHD events.

Harms: We found no RCTs.

Comment: None.

OPTION STATINS IN PEOPLE AT HIGH RISK

Mortality

Compared with placebo/usual care Pravastatin seems more effective than placebo at reducing mortality at 5 to 15 years in men with dyslipidaemia (moderate-quality evidence).

CVD events

Compared with placebo/usual care Pravastatin may be more effective than placebo at reducing the composite outcome of non-fatal MI and death from CHD at 5 to 15 years in men with dyslipidaemia, but we don't know whether it is more effective at reducing the composite outcome of CHD mortality, non-fatal MI, or stroke at 3 years in older people, or at reducing the composite outcome of cardiovascular mortality or hospital admission for cardiovascular morbidity at 46 months in people with microalbuminuria (low-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

We found one systematic review (search date 2005, 7 RCTs, 42,848 people) that assessed statins for primary prevention of CVD in people at low, medium, or high risk of CVD (not limited to those with dyslipidaemia). [8] The RCTs included in the review were conducted primarily (90%) in people who did not have apparent CVD. The review did not report results separately for different levels of CHD risk, and so we report results from individual RCTs in people with dyslipidaemia and at high risk of CHD (2 RCTs; 9834 people). [18] [19] Two RCTs (5749 people) were in people with diabetes, a population that is not within the scope of this review and so these RCTs are not discussed further. One RCT (10,305 people) was in people not deemed to be conventionally dyslipidaemic and so is not discussed further. See Comments section of statins in people at low risk of CHD, p 4 for details of the analysis carried out by the review.

The first RCT (6595 men, age 45–64 years, mean plasma cholesterol 272 mg/dL, equivalent to 7.0 mmol/L) identified by the review found that pravastatin 40 mg daily significantly reduced the combined outcome of non-fatal MI or CHD mortality at 5 years compared with placebo (174/3302 [6%] with pravastatin *v* 248/3293 [8%] with placebo; RR 0.69, 95% CI 0.57 to 0.83). [18] It found that pravastatin reduced all-cause mortality compared with placebo but the reduction was of borderline significance (106/3302 [3%] with pravastatin *v* 135/3293 [4%] with placebo; RR 0.78, 95% CI 0.60 to 1.00).

A long-term follow-up report of the RCT [18] found that pravastatin significantly reduced all-cause mortality (619/3302 [19%] with pravastatin *v* 674/3293 [21%] with placebo; HR 0.88, 95% CI 0.79 to 0.99) and the composite outcome of non-fatal MI and fatal CHD at 15 years' follow-up (390/3302 [12%] with pravastatin *v* 509/3293 [16%] with placebo; HR 0.73, 95% CI 0.63 to 0.83; P <0.001). [20] The study concluded that 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years. [20] The proportion of men taking a statin at 5 years after the end of the initial phase of the RCT was significantly higher among men originally assigned to pravastatin compared with placebo (39% with pravastatin *v* 35% with placebo; P <0.001; absolute numbers not reported).

The second RCT (5804 men and women, age 70–82 years, at high risk of developing CVD and stroke) identified by the review included people with vascular disease but reported a subgroup analysis of people with no history of vascular disease (3289 people). [19] The RCT found no significant difference between pravastatin 40 mg daily and placebo in the composite outcome of CHD death or non-fatal MI or stroke at 3 years in people with no vascular disease (181/1585 [11%] with pravastatin *v* 200/1654 [12%] with placebo; HR 0.94, 95% CI 0.77 to 1.15).

We found one additional RCT (864 adults aged 28–75 years with microalbuminuria, mean cholesterol level 5.8 ± 1.0 mmol/L, mean systolic/diastolic blood pressure 130 ± 18/76 ± 10 mm Hg, and median urinary albumin excretion 22.8 [15.8–41.3] mg/24 hours) that examined the effect of pravastatin (433 people) 40 mg daily versus placebo (431 people). [21] It found no significant difference in the combined outcome of cardiovascular mortality or hospital admission for cardiovascular morbidity over 46-months of follow-up (RR 0.87, 95% CI 0.49 to 1.57; P = 0.6; absolute numbers not reported). A subgroup analysis of the RCT, restricted to people with metabolic syndrome (286 people), found that pravastatin significantly reduced major cardiac events compared with placebo (6% with pravastatin *v* 12% with placebo; absolute numbers not reported; HR 0.39, 95% CI 0.17 to 0.89; P = 0.02). [22]

Harms:

The first RCT found no significant difference between pravastatin and placebo in fatal or non-fatal cancers (116/3302 [3.5%] with pravastatin *v* 106/3293 [3.2%] with placebo; P = 0.55). [18] The long-term follow-up study found no significant difference between the pravastatin and placebo groups in the proportion of men with a first incident cancer at 15 years (431/3291 [13%] with pravastatin *v* 404/3286 [12%] with placebo; HR 1.05, 95% CI 0.92 to 1.20; P = 0.50). [20]

The second RCT found that a similar proportion of people reported "serious adverse effects" with both pravastatin and placebo (1608/2891 [56%] with pravastatin *v* 1604/ 2913 [55%] with placebo; significance not assessed). [19] The adverse effects were not specified.

The additional RCT reported similar rates of premature discontinuation because of intolerability for pravastatin and placebo (13/433 [3%] with pravastatin *v* 22/431 [5%] with placebo). [21]

Comment:

Clinical guide:

See comments in Statins in people at low risk of CHD, p 4 .

QUESTION **What are the effects of reduced- or modified-fat diet in people at low, medium, or high risk of CHD?**

OPTION **REDUCED- OR MODIFIED-FAT DIET IN PEOPLE AT LOW, MEDIUM, OR HIGH RISK**

Mortality

Compared with no dietary modification A reduced- or modified-fat diet is no more effective than control at reducing mortality in people at risk of CHD events (high-quality evidence).

CVD events

Compared with no dietary modification A reduced- or modified-fat diet may be more effective than control at reducing cardiovascular events in people at risk of CHD events but a low total-fat diet (low in fat and high in vegetables, fruits, and grains) seems no more effective than no dietary modification at reducing total CVD in postmenopausal women aged 50 to 79 years (moderate-quality evidence).

For GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia, see table, p 15 .

Benefits:

Reduced- or modified-fat diet versus no dietary modification:

We found one systematic review [23] and two subsequent RCTs. [24] [25] The systematic review (search date 1999, 27 RCTs) assessed the effect of reduced or modified-fat diet (diet advice, advice plus a supplement, or diet provided) on cardiovascular events. [23] The RCTs included in the review were conducted in people at high and low risk of cardiovascular events. In the review, initial levels of risk were generally high (in control groups, people at low risk had 2.57 events per 100 people per year, and people at high risk had 7.62 events per 100 people per year). Overall, the review found no significant difference between diet and control in all-cause mortality (RR 0.98, 95% CI 0.86 to 1.12). It found that the diet significantly reduced cardiovascular events for all people (RR 0.84, 95% CI 0.72 to 0.99). Relative risks for combined cardiovascular events were similar for people at high or low risk of cardiovascular events (RR for high-risk people 0.84, 95% CI 0.70 to 0.99; RR for low-risk people 0.82, 95% CI 0.56 to 1.20). The review found that, after excluding one RCT that used fish oil in addition to dietary advice, there was no significant difference between treatments for total mortality, cardiovascular mortality, or cardiovascular events (RR for total mortality 1.02, 95% CI 0.91 to 1.14; RR for cardiovascular mortality 0.94, 95% CI 0.79 to 1.11; RR for combined cardiovascular events 0.86, 95% CI 0.72 to 1.03). The effect of diet on combined cardiovascular events was greater for RCTs with mean follow-up >2 years (>2 years: RR 0.76, 95% CI 0.65 to 0.90; <2 years: RR 0.96, 95% CI 0.75 to 1.23). The only low-risk trials were in institutionalised people using controlled diets. Other types of diets, such as the Mediterranean diet, have not been well studied in people without known CVD. [23]

The first subsequent RCT (104 healthy men, aged 40–49 years [in 1972], with combined hyperlipidaemia, baseline values of total serum cholesterol >6.45 mmol/L, and fasting triglycerides >2.55 mmol/L) compared the effect of a 5-year diet intervention versus that of control (type not reported) on 24-year mortality. [24] The RCT found that the 5-year diet (emphasis on reduction in saturated fat and increase in polyunsaturated fat consumption) significantly reduced mortality at year 24 compared with control (12/55 [22%] deaths with 5-year diet *v* 21/49 [43%] deaths with control; RR 0.49, 95% CI 0.22 to 0.91; P = 0.02).

The second subsequent RCT (48,835 postmenopausal women aged 50–79 years) compared the effects of a dietary intervention (low-fat and high vegetable, fruit, and grain) versus those of usual diet on total CVD. [25] The RCT found no significant difference in rate of total CVD at year 8 between

the dietary intervention group and usual diet group (1357/19,541 [7%] with dietary intervention *v* 2088/29,294 [7%] with usual diet; HR 0.98, 95% CI 0.92 to 1.05; P value not reported), despite a reduction in fat intake of 8% on average.

Harms: **Reduced- or modified-fat diet versus no dietary modification:**
The systematic review [23] and two RCTs [24] [25] gave no information on adverse events.

Comment: None.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence 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.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SUBSTANTIVE CHANGES

Ezetimibe in people at low risk New option for which we identified no systematic review or RCTs in people at low risk of CHD events. Categorisation set at Unknown effectiveness.

Ezetimibe in people at medium risk New option for which we identified no systematic review or RCTs in people at medium risk of CHD events. Categorisation set at Unknown effectiveness.

Ezetimibe in people at high risk New option for which we identified no systematic review or RCTs in people at high risk of CHD events. Categorisation set at Unknown effectiveness.

Statins in people at high risk of CHD A long-term follow-up report of one previously reported RCT [18] in men with hypercholesterolaemia and no history of MI found that pravastatin reduced the composite outcome of non-fatal MI and fatal CHD at 15 years' follow-up. [20] Categorisation unchanged (Beneficial).

Statins in people at low risk of CHD One further report [10] of an already reported RCT [9] analysed data in women alone. The RCT found no significant difference between pravastatin plus cholesterol-lowering diet and cholesterol-lowering diet alone in rate of CHD events at 5 years in women at low risk of CHD, although the rate was lower with addition of pravastatin. [10] The RCT found that the reduction in rate of CHD associated with addition of pravastatin to a cholesterol-lowering diet was greater in older women (aged 60 years or older), but the difference between groups remained non-significant. Categorisation unchanged (Likely to be beneficial).

Resins in people at medium risk Existing evidence re-evaluated. Benefit of cholestyramine unclear; evidence presented in only men and may not be generalisable. Categorisation changed from Likely to be beneficial to Unknown effectiveness.

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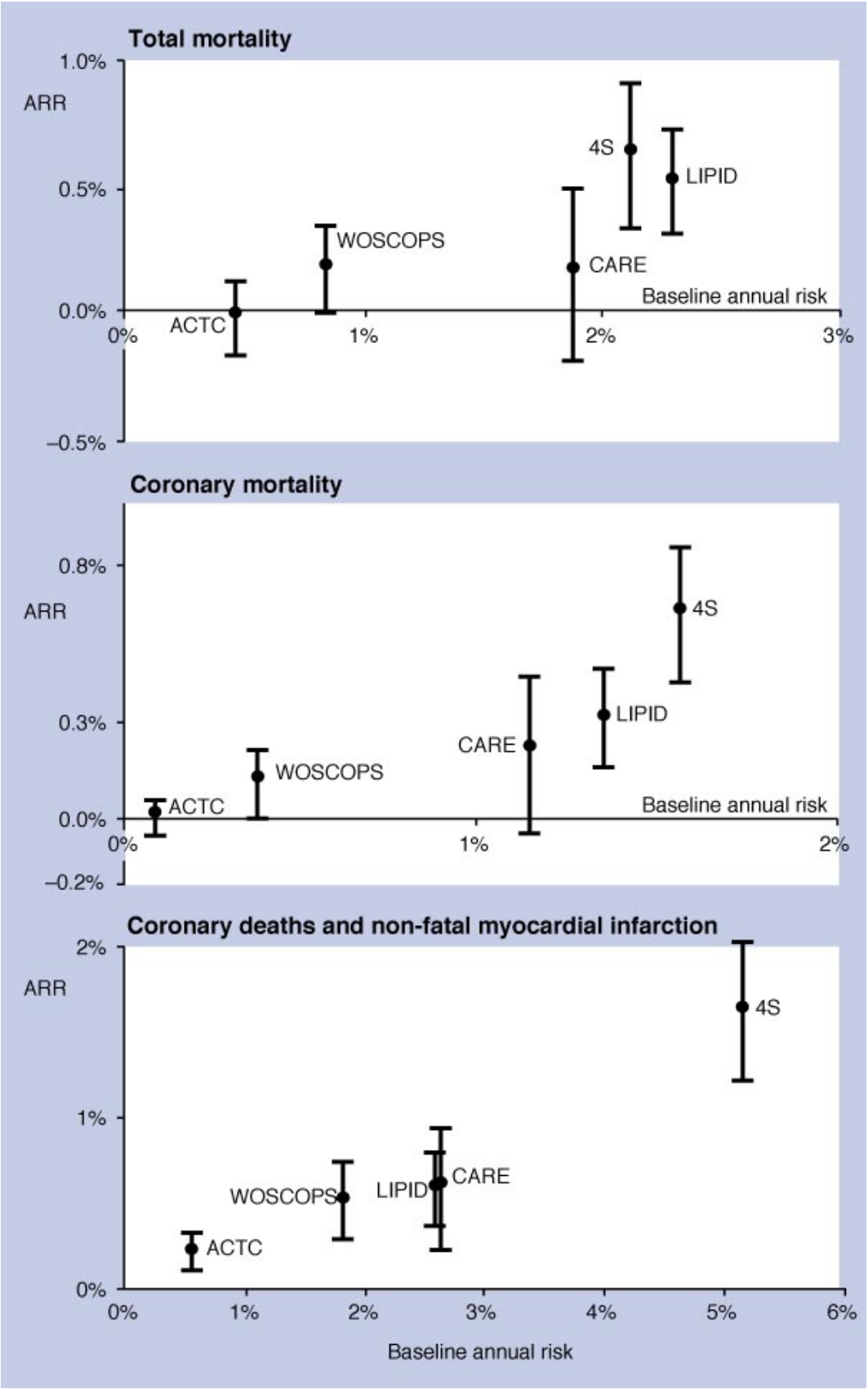

FIGURE 1 **Effects of cholesterol lowering: relation between the ARR (for annual total mortality, CHD mortality, coronary deaths, and non-fatal MI) and the baseline risk of those events in the placebo group for 5 large statin trials in primary and secondary care settings (ACTC = AFCAPS/TexCAPS, 4S, LIPID, CARE, WOSCOPS).**

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TABLE **GRADE evaluation of interventions for primary prevention of CVD: treating dyslipidaemia**

Important outcomes	**CVD events, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of pharmacological cholesterol-lowering interventions in people at low risk (<0.6% annual CHD risk)?									
1 (7832) [9] [10]	CVD events	Statin plus cholesterol-lowering diet *v* cholesterol-lowering diet alone (low risk)	4	0	0	–1	0	Moderate	Directness point deducted for use of an active co-intervention (cholesterol-lowering diet)
What are the effects of pharmacological cholesterol-lowering interventions in people at medium risk (0.6–1.4% annual CHD risk)?									
1 (4081) [13] [14]	Mortality	Fibrates *v* placebo (medium risk)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (4081) [13] [14]	CVD events	Fibrates *v* placebo (medium risk)	4	0	0	0	0	High	
1 (3806) [15]	CVD events	Resins *v* placebo (medium risk)	4	0	0	–2	0	Low	Directness points deducted for uncertainty of benefit of treatment and narrow population (only men)
2 (16,960) [16] [17]	Mortality	Statins *v* placebo/usual care (medium risk)	4	0	0	–2	0	Low	Directness points deducted for one RCT not being powered to detect a difference between groups, uncertainty of benefit in one RCT (due to high rate of conversion from placebo to statin), and inclusion of some people with history of CVD in one RCT
2 (16,960) [16] [17]	CVD events	Statins *v* placebo/usual care (medium risk)	4	0	0	–2	0	Low	Directness points deducted for uncertainty of benefit in one RCT (due to high rate of conversion from placebo to statin) and inclusion of some people with history of CVD in one RCT
What are the effects of pharmacological cholesterol-lowering interventions in people at high risk (1.5% or more annual CHD risk)?									
1 (6595) [18] [20]	Mortality	Statins *v* placebo (in people at high risk)	4	0	0	–1	0	Moderate	Directness point deducted for narrow population (only men)
3 (13,263) [18] [20] [19] [21]	CVD events	Statins *v* placebo (in people at high risk)	4	–1	0	–1	0	Low	Quality point deducted for methodological limitations (subgroup analysis in one RCT and incomplete reporting of results in one RCT). Directness point deducted for narrow populations (only men in one RCT, and only older people in one RCT)
What are the effects of reduced- or modified-fat diet in people at low, medium, or high risk of CHD?									
At least 27 RCTs (at least 48,939) [23] [24]	Mortality	Reduced- or modified-fat diet *v* no dietary modification	4	0	0	0	0	High	
28 RCTs (at least 48,835) [23] [25] [24]	CVD events	Reduced- or modified-fat diet *v* no dietary modification	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results

Important outcomes	CVD events, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio