Statins for the primary prevention of cardiovascular disease (Review)

Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S

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[Intervention Review]

Statins for the primary prevention of cardiovascular disease

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ABSTRACT

Background

Reducing high blood cholesterol, a risk factor for cardiovascular disease (CVD) events in people with and without a past history of coronary heart disease (CHD) is an important goal of pharmacotherapy. Statins are the first-choice agents. Previous reviews of the effects of statins have highlighted their benefits in people with coronary artery disease. The case for primary prevention, however, is less clear.

Objectives

To assess the effects, both harms and benefits, of statins in people with no history of CVD.

Search strategy

To avoid duplication of effort, we checked reference lists of previous systematic reviews. We searched the Cochrane Central Register of Controlled Trials (Issue 1, 2007), MEDLINE (2001 to March 2007) and EMBASE (2003 to March 2007). There were no language restrictions.

Selection criteria

Randomised controlled trials of statins with minimum duration of one year and follow-up of six months, in adults with no restrictions on their total low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol levels, and where 10% or less had a history of CVD, were included.

Data collection and analysis

Two authors independently selected studies for inclusion and extracted data. Outcomes included all cause mortality, fatal and non-fatal CHD, CVD and stroke events, combined endpoints (fatal and non-fatal CHD, CVD and stroke events), change in blood total cholesterol concentration, revascularisation, adverse events, quality of life and costs. Relative risk (RR) was calculated for dichotomous data, and for continuous data pooled weighted mean differences (with 95% confidence intervals) were calculated.

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Main results

Fourteen randomised control trials (16 trial arms; 34,272 participants) were included. Eleven trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (RR 0.83, 95% CI 0.73 to 0.95) as was combined fatal and non-fatal CVD endpoints (RR 0.70, 95% CI 0.61 to 0.79). Benefits were also seen in the reduction of revascularisation rates (RR 0.66, 95% CI 0.53 to 0.83). Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no clear evidence of any significant harm caused by statin prescription or of effects on patient quality of life.

Authors' conclusions

Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

PLAIN LANGUAGE SUMMARY

Statins for the primary prevention of cardiovascular disease

Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity world wide. Reducing high blood cholesterol which is a risk factor for CVD events is an important goal of medical treatment. Statins are the first-choice agents. Since the early statin trials were reported, several reviews of the effects of statins have been published highlighting their benefits particularly in people with a past history of CVD. However for people without a past history of CVD (primary prevention), the evidence is less clear. The aim of this systematic review is to assess the effects, both in terms of benefits and harms of statins for the primary prevention of CVD. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE until 2007. We found 14 randomised control trials with 16 trial arms (34,272 patients) dating from 1994 to 2006. All were randomised control trials comparing statins with usual care or placebo. Duration of treatment was minimum one year and with follow up of a minimum of six months. All cause mortality. coronary heart disease and stroke events were reduced with the use of statins as was the need for revascularisations. Statin treatment reduced blood cholesterol. Taking statins did not increase the risk of adverse effects such as cancer. and few trials reported on costs or quality of life. This current systematic review highlights the shortcomings in the published trials and we recommend that caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

BACKGROUND

Burden of cardiovascular disease

Cardiovascular disease (CVD) encompasses a wide range of disease including ischaemic heart disease, coronary heart disease (e.g. heart attack), cerebrovascular disease (e.g. stroke), raised blood pressure, hypertension, rheumatic heart disease and heart failure. The major causes of CVD are unhealthy diets, tobacco use and physical inactivity (WHO 2008).

CVD is ranked as the number one cause of mortality and is a major cause of morbidity world wide accounting for 17 million deaths, 30% of total deaths. Of these, 7.6 million are due to heart attacks and 5.7 million due to stroke (WHO 2008). Over 80% of CVD deaths occur in low and middle income countries (WHO 2008). In developing countries, it causes twice a many deaths as HIV, malaria and tuberculosis combined (Gaziano 2007). It has been estimated that between 1990 and 2020, the increase in ischaemic heart disease alone will increase by 29% in men and 48% in women in developed countries and by 120% in women and 127% in men in developing countries (Yusuf 2001). CVD imposes high social costs, including impaired quality of life and reduced economic activity, and accounts for a large share of health service resources (Gaziano 2007).

CVD is multi-factorial in its causation and lifestyle changes are the basis of any treatment strategy, with patients often requir-

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ing behavioural counselling. Those unable to achieve or maintain adequate risk reduction on lifestyle changes alone or those at high risk patients require pharmacotherapy. Reducing high blood cholesterol (hypercholesterolaemia), a risk factor for both fatal and non-fatal CVD events in people with and without a past CVD, is an important goal of pharmacotherapy (Prospective Studies Collaboration 2007). Statins are the first-choice agents for Low Density Lipoprotein Cholesterol (LDL-C) reduction. The level at which blood cholesterol is treated is more dependent on the absolute reduction in risk that can be expected, given the patient's other risk factors, and taking into account the resources available for prevention (Ramsay 1996). Since the relation between blood cholesterol and cardiovascular risk is a continuous one (Chen 1991) (although J-shaped in some studies for total mortality), there is no definite threshold above which patients must be treated a priori. If a threshold for 'high' cholesterol is set at over 3.8 mmol/L, (146.9 mg/dL) this would contribute 4.4 million deaths worldwide and 40.4 million DALYs (disability adjusted life years) (Ezzati 2002). Furthermore, the average level of blood cholesterol within a population is an important determinant of the CVD risk of the population. Differences in average levels of blood cholesterol between populations are largely determined by differences in diet, and countries with high dietary saturated fat intake and a low ratio of polyunsaturated to saturated fatty acids have higher than average cholesterol levels (Davey Smith 1992).

Trial evidence

Since the early statin trials were reported, several reviews of the effects of statins have been published highlighting the benefits of their use (Bartlett 2003; Blauw 1997; Briel 2004; Cheung 2004; Ebrahim 1999; Katerndahl 1999; LaRosa 1994; LaRosa 1999; Law 2003; Pignone 2000; Silva 2006; Thavendiranathan2006; Ward 2007; Wilt 2004). In particular, an individual patient data review and meta-analysis of 90,056 participants in 14 large randomised controlled trials (RCTs) including the large Heart Protection Study (HPSCG 2003), followed up for 5 years, concluded that statins were beneficial in reducing the risk of CVD events in people at risk, and showed consistency of treatment benefits across a wide range of patient subgroups (Baigent 2005). The evidence on the beneficial effects of statins has led expert committees to promote their use on a global scale particularly in the developed world. (Manuel 2006; NICE 2006). Statin prescribing and expenditure have risen rapidly as a result. For example, the European average (weighted by population of each country) increased from 11.12 defined daily doses/1000 in 1997 to 41.80/1000 in 2002, an average 31% increase a year (Walley 2004). The expenditure on statin drugs in England was over £20 million in 1993, over £113 million in 1997 (Ebrahim 1998) and has risen to more than £500 million in 2006 (NICE 2006).

Adverse effects of lowering cholesterol with statins

There has been some concern that low levels of blood cholesterol increase the risk of mortality from causes other than coronary heart disease, including cancer, respiratory disease, liver disease and accidental/violent death. Several studies have now demonstrated that this is mostly, or entirely, due to the fact that people with low cholesterol levels include a disproportionate number whose cholesterol has been reduced by illness - early cancer, respiratory disease, gastrointestinal disease and alcoholism, among others (Iribarren 1997; Jacobs 1997). Thus it appears to be the pre-existing disease which causes both the low cholesterol and raised mortality (Davey Smith 1992).

The potential adverse effects of statins among people at low risk of CVD are poorly reported and unclear (Jackson 2001) but, among those with pre-existing CVD, the evidence suggests that any possible hazards are far outweighed by the benefits of treatment. Two reviews of 18 and 35 trials respectively found that there were similar rates of serious adverse events with statins as compared to placebo (Kashani 2006; Silva 2006) and a further review of 26 RCTs concluded that there was no effect on risk of cancer with statins (Dale 2006). Other adverse events have been investigated and may be causal, for example rhabdomyolysis - break down of muscles - which can be serious if not detected and treated early (Beers 2003). However, in a systematic review of statins with about 35,000 people and 158,000 person years of observation in both treated and placebo groups, rhabdomyolysis was diagnosed in eight treated and five placebo patients, none with serious illness or death (Law 2003). One RCT of 621 adults found that statins did not adversely affect self reported quality of life, mood, hostility psychological well being or anger expression (Wardle 1996). Small decrements in scores on tests of psychomotor speed and attention were found by Muldoon *et al* in an RCT of 209 adults, but Muldoon concluded that more research is needed to fully evaluate this (Muldoon 2000). In addition, a systematic review of five statin trials (N = 30,817) found no evidence that statins increased risk of death from non-illness mortality (accidents, violence or suicide) (Muldoon 2001).

Limitations of the reviews of the effects of statins

A major limitation of the evidence summaries to date is the emphasis of the use of statins in secondary prevention of CVD without distinguishing between findings in primary prevention trials. More recently, however, a number of systematic reviews have focused their attention of the use of statins in primary prevention but they differ in their interpretation of the evidence to date (Brugts 2009; Ebrahim 1999; Mills 2008; NICE 2006; Thavendiranathan2006; Vrecer, 2003; Ward 2007). This is largely due to the differing inclusion criteria of the reviews and differences in reporting of out-

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comes. Where the most recent systematic review (Baigent 2005, Brugts 2009; Mills 2008) promote the use of statins in the primary prevention of CVD (the latter team of authors received industry sponsorship), the evidence remains less clear leading other authors to conclude that the assumed benefits of statin therapy in secondary prevention trials should not be extrapolated to primary prevention populations and that current cholesterol treatment guidelines based on this assumption need to be revised (Abramson 2007).

The aim of this systematic review is to assess the effects of statins for primary prevention of CVD. We planned to look for adverse events associated with statins and examine effects in populations such as elderly people and women.

OBJECTIVES

To assess the effects, both harms and benefits, of statins in people with no history of CVD events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing treatment with statins for at least 12 months with placebo or usual care. Length of follow-up of outcomes had to be at least six months.

Types of participants

Men and women (aged 18 or more) with no restrictions on total, low or high density lipoprotein cholesterol levels. We limited our inclusion of study population to have less or equal to 10% of a previous history of CVD.

Types of interventions

Statins (HMG CoA reductase inhibitors) versus placebo or usual care.

Concommitant interventions

Drug treatments and other interventions were accepted provided they are given to both arms of the intervention groups. Adjuvant treatments with one additional drug where a patient developed excessively high lipids during the trial were accepted.

Types of outcome measures

The following outcomes were collected:

- death from all causes;
- fatal and non-fatal CHD, CVD and stroke events;
- combined endpoint (fatal and non-fatal CHD, CHD and stroke events);
- change in blood total cholesterol concentration;
- revascularisation;
- adverse events;
- quality of life;
- costs.

Search methods for identification of studies

As previous comprehensive reviews (Bartlett 2005; Ebrahim 1999; Ward 2007) have been undertaken we built on this work. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue1, 2007), MEDLINE (2001 to March 2007) and EMBASE (2003 to March 2007). A standard RCT filter was used for MEDLINE (Dickersin 1994) and EMBASE (Lefebvre 1996). No language restrictions were applied to either searching or trial inclusion. See Appendix 1 for search strategies. Reference lists of identified review articles and of all included RCTs were searched to find other potentially eligible studies.

Data collection and analysis

Trial selection

Two reviewers independently read the results from searches on electronic databases to identify those articles relevant to this systematic review based on title or title and abstract. Full articles were retrieved for further assessment. The articles were read independently by two reviewers and a form was designed to describe the characteristics of studies to be included or excluded as set out in the recommendations in the Cochrane Handbook 5.0.2 (Higgins 2009).

Assessment of risk of bias

We used criteria described in the Cochrane Handbook of Systematic Reviews 5.0.2 (Higgins 2009) to describe the quality of trials we found. Two authors independently assessed methodological quality of selected studies (FT, KW). Any differences of opinion were resolved by discussion and consensus and finally by discussion with a third author (SE). To assess any risk of bias we focused on the following dimensions as recommended in the Cochrane Handbook:

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1. Adequate sequence generation (such as computer generated random numbers and random number tables, whilst inadequate approaches included the use of alternation, case record numbers, birth dates or days of the week).
2. Adequate measures to conceal allocation. Concealment was deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients.
3. Blinding was deemed adequate if blinding was applied (whether the participant, care provider or outcome assessors)
4. Completeness of outcome data was deemed adequate if intention to treat analysis was performed for each outcome and not what patient numbers the analysis was confined to.
5. Free of selective reporting: was deemed adequate if all stated outcomes were reported on and presented. We will highlight any selective outcome reporting.
A risk of bias graph for each trial was made available to assess quality.

Data extraction

A data extraction form was designed and included:

- study ID;
- quality;
- participant baseline characteristics;
- intervention dosage and duration.

To assess baseline risk of CVD the following median/mean values were also extracted:

- age;
- gender ratio;
- proportion of current smokers;
- total cholesterol, HDL and LDL cholesterol.

Outcome measures extracted included:

Primary outcome measures

- death from all causes;
- fatal and non-fatal CHD events,
- fatal and non-fatal CVD events
- fatal and non-fatal stroke events;
- combined endpoint (fatal and non-fatal CHD, CHD and stroke events);

Secondary outcome measures

- change in blood total cholesterol concentration;
- revascularisation;
- adverse events;
- quality of life.
- costs.

Data was extracted by two reviewers independently (FT, KW). Any differences of opinion were resolved by discussion and consensus and finally by discussion with a third reviewer (SE).

Contacting trialists

For unpublished studies or where data was incomplete in published papers, attempts were made to contact the authors to obtain further details.

Data analysis

Relative risk (RR) and 95% confidence intervals (CI) were calculated for dichotomous data. Quantitative analyses of outcomes was based on 'intention to treat' (ITT). For continuous data (such as change in blood total cholesterol), pooled weighted mean differences (with 95% CI) were calculated.
We did not add the number of fatal and non-fatal clinical events together from any of the studies that we included in this review as it was not possible to ascertain whether an individual who had a non-fatal clinical event followed by a fatal clinical event was counted as a clinical event under both categories. As a result we have only included the composite of fatal and non-fatal clinical events if this was reported in the papers. For example, number of stroke events: seven trials reported this as a composite outcome, one reported on fatal and one on non-fatal stroke events. We did not add the fatal and non-fatal strokes together to ascertain a composite number.

Heterogeneity

Because trials found may not have been carried out according to a common protocol there will usually be variations in patient groups, clinical settings, concomitant care etc. We, therefore, assessed heterogeneity between trial results. Trial data was considered to be heterogeneous where the I^2 statistic was > 50%. For analysis we used the conservative, fixed effects method unless where data was heterogenous in which case we used the random effects model. Where significant heterogeneity was present, we attempted to explain the differences based on the patient clinical characteristics and interventions of the included studies.

Publication or other bias

A funnel plot was used to test for the presence of publication bias based on the data for the primary outcome of all cause mortality. Publication bias is usually detected by asymmetry of the funnel plot (Sterne 2001).
Analyses for potential effect modifiers was initially considered but abandoned due to lack of adequate reporting. These were to included:

- gender;

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- extent of hyperlipidaemia;
- age under 65, 65 and over.

Sensitivity analysis

Sensitivity analysis was used to explore the influence of the following on effect size:

- repeating analysis taking account of study quality;
- repeating analysis excluding any very long/large studies to see how they influence the results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

After removal of duplicates, 4227 references were identified. From reading titles and abstracts 4128 were eliminated as being not relevant to the review. Full papers were obtained for 99 references. From these 99 papers, 72 papers reporting on 48 studies were excluded (see Characteristics of excluded studies). A total of 27 papers reporting on 14 trials were included (see Characteristics of included studies). Checking the references of the recent systematic reviews found 1 further trial (JUPITER 2008) which was published outside the dates of our search, details of which are listed in the Table: Characteristics of studies awaiting classification. Of the 14, trials, two tested two different interventions; for the purpose for meta analysis, each trial was counted as two trials (in total 16 trial arms) (CELL A 1996; CELL B 1996; PHYLLIS A 2004; PHYLLIS B 2004). The trials dated from 1994 to 2006 and were conducted world-wide, mainly in industrially developed countries (Japan, USA and Europe). Twelve trials recruited patients with specific conditions: eight recruited participants with raised lipids, three with diabetes, two with hypertension and one with microalbuminuria

All tested the effectiveness of a statin compared with placebo; nine tested pravastatin 10-40mg per day; one atorvastatin 10mg per day; two fluvastatin 40-80mg per day; two lovastatin 20-40mg per day and the remaining simvastatin 40mg per day. Five trials also included advice, counselling or information on health behaviour modification such as diet, smoking cessation, exercise.

In total, the 14 trials (with 16 trial arms) recruited 34,272 participants and observed outcomes ranging from 1-5.3 years, amounting to approximately 113,000 patient years. The size of the population recruited ranged from 47- 8,009. The mean age of the participants was 57 years (range 28-80 years), 65.9% were male and of the five trials which reported on ethnicity; 91.4 % were Caucasian.

Two trials (AFCAPS/TexCAPS 1998 and CARDS 2004) were stopped prematurely because significant reductions in primary composite outcomes between the intervention and placebo had been observed. These trials had recruited 27.1% of the total study population and were stopped 1.4-2.0 years before the official end date. We were unable to estimate the number of potential patients years of observation lost due to incomplete provision of data.

Data on all cause mortality was provided in eight trials. Excluding the two trials whose primary outcome was change in size of carotid artery, eight of the remaining trials chose a composite outcome as their primary outcome. Despite this, seven provided data on fatal and six on non-fatal CHD events and two on fatal and one on non-fatal CVD events. Whilst eight trials reported on combined stroke events, one provided data on non-fatal and one on fatal stroke events. Nine trials provided data on cholesterol and seven on adverse events. One provided economic costings, one provided data on patient perceived quality of life Five trials provided data on compliance: of those on statins, compliance ranged from 67%-92% whilst for those on placebo 53%-93%.

Excluding the 3 trials which solely recruited participants with diabetes; 1-20% accounted for diabetics the other trials. Excluding the two trials which recruited participants with hypertension; the remaining studies had recruited 15-67% with hypertension. The proportion of participants smoking ranged from 10-44% in the 13 trials which provided this data. We were unable to ascertain baseline lipid levels for three trials. Baseline total cholesterol levels ranged from 5.00-6.97 mmol/l (median 6.05 mmol/l), HDL cholesterol from 1.07-1.46 mm/l (median 1.24 mm/l) and LDL cholesterol from 2.92-4.95 mm/l (median 3.95mm/l).

Risk of bias in included studies

Four of the 16 trial arms did not provide adequate information on the methods used for randomisation, three of which had recruited more than 2000 participants. Fourteen trials used blinding to reduce bias, 10 of which used double blinding methods. Ten used intention to treat analysis and the drop out rates for those that did apply was ranged from 2-17% (only two trials provided such data). We judged 13 of the trials to be free from selective bias. (Figure 1; Figure 2). The MRC/BHF only provided data on total CVD events for patients with diabetes in the primary prevention group, whilst HYRIM did not present baseline and four-year follow-up data on cholesterol.

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Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

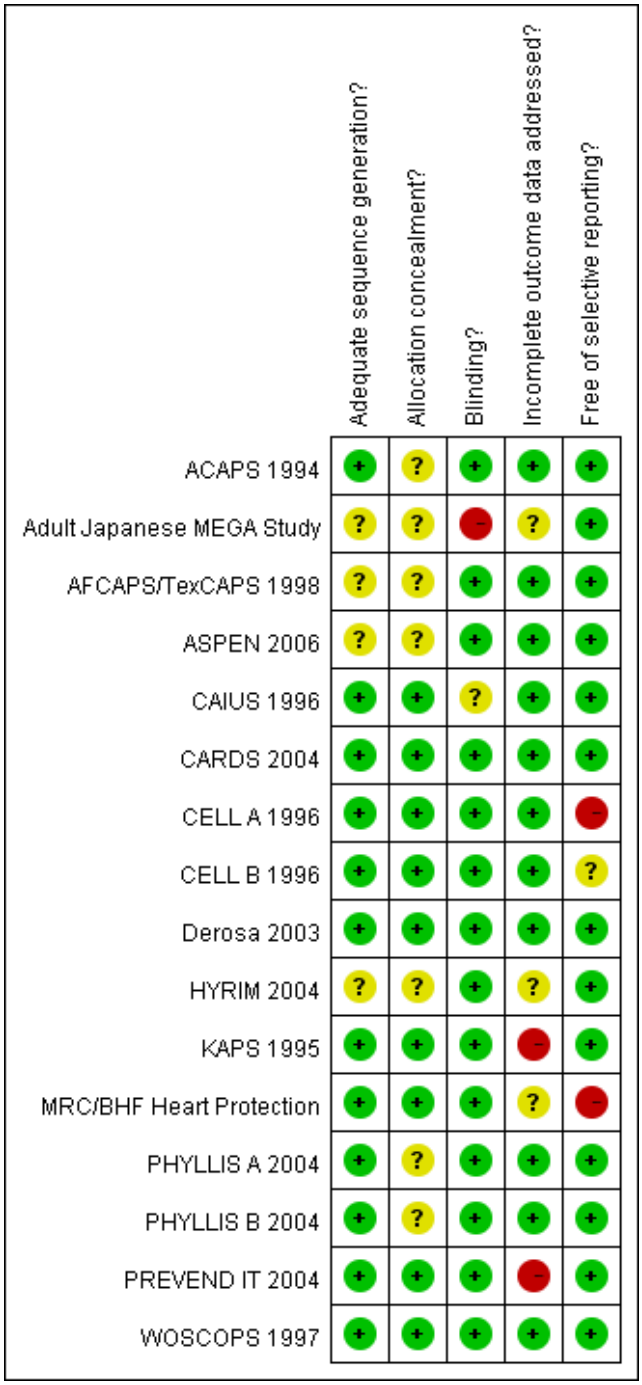

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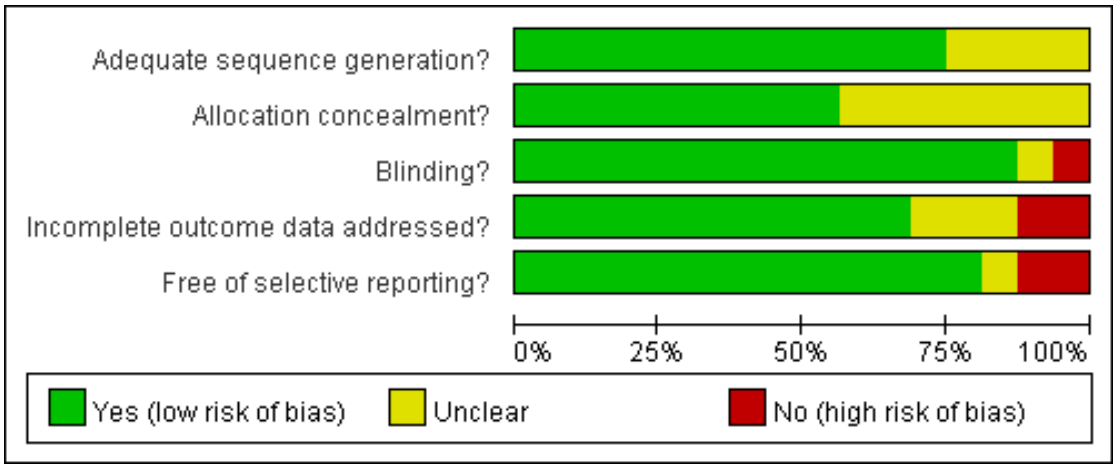
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



The funnel plot for all cause mortality showed no sign of publication bias (Figure 3). Only one trial was funded from taxation (Ministery of Health) whilst the authors of nine trials reported having been sponsored either fully or partially by pharmaceutical companies (five by Bristol Myers and Squibb; two by Pfizer).

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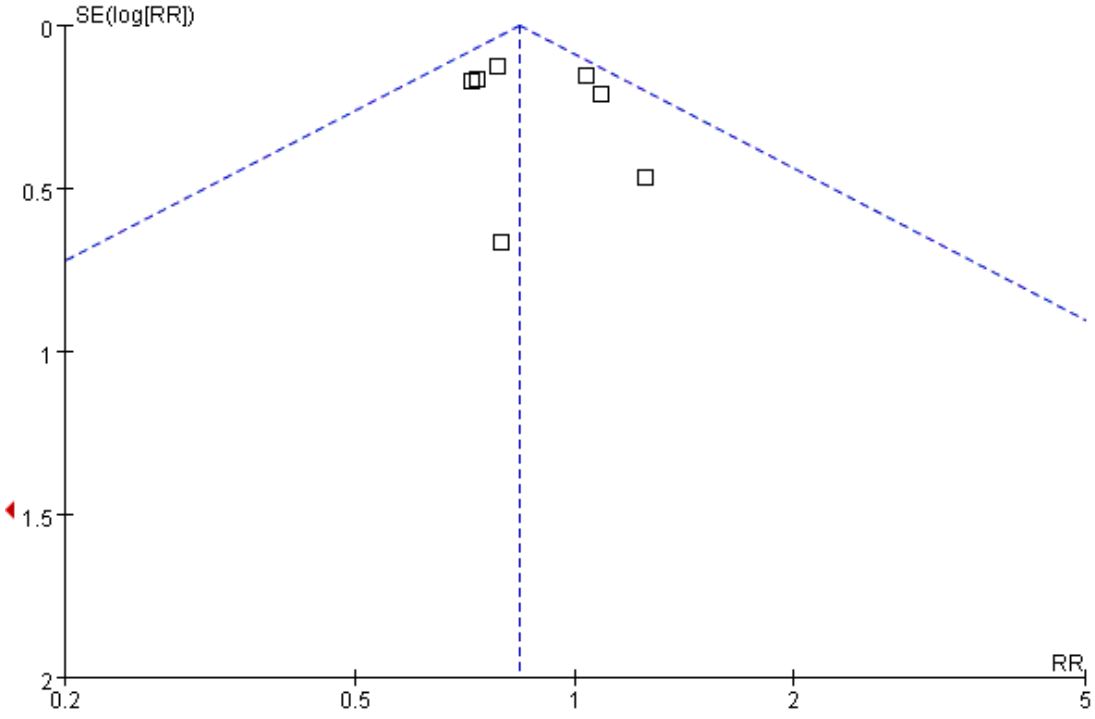
Figure 3. Funnel plot of comparison: 2 Mortality and Morbidity, outcome: 2.1 Total Mortality.



Effects of interventions

All cause mortality (Analysis 2.1):

Eight trials with 28,161 participants recruited reported on total mortality. During observation, 794 (2.8%) died with a death rate of 1.0 per 100 person years of observation in the control groups. None of the individual trials showed strong evidence of a reduction in total mortality but when the data were pooled using a fixed effects model, a relative risk reduction which favoured statin treatment by 17% was observed: RR 0.83 (95% CI 0.73-0.95). No heterogeneity was observed.

Fatal and non-fatal CHD events (Analysis 2.2, Analysis 2.3 and Analysis 2.4)

Nine trials with 10 arms and 27,969 participants reported on combined fatal and non-fatal CHD events: Four trials showed evidence of a reduction in this combined outcome which was maintained in the pooled analysis using a fixed effects model: 1,577 (5.63%) events; RR 0.72 (95% CI 0.65-0.79).

Observations on fatal or non-fatal CHD events are based on less than 55% of the participants recruited. Of the two trials which had been stopped prematurely, only AFCAPS/TexCAPS presented data on fatal CHD events. No significant risks reduction were observed in fatal CHD events; 85/8823 (0.9%); RR 0.78 (95% CI 0.59-1.04) nor non-fatal CHD events 94/4927 (1.9%) non-fatal CHD events; RR 0.74 (95% CI 0.50-1.10). No heterogeneity was observed. .

Fatal and non-fatal CVD events (Analysis 2.5, Analysis 2.6 and Analysis 2.7)

Six trials with 12,286 participants reported on combined fatal and non-fatal CVD events. Two of the larger trials with 11,343 participants were able to demonstrate a significant reduction in this combined outcome and this was maintained in the pooled analysis using fixed effects model: 845 (6.8%) events; RR 0.74 (95% CI 0.66-0.85). There was no significant heterogeneity.

Two trials reported on fatal and one on non-fatal CHD events. Reductions in risk were observed in these endpoints; fatal CVD events;131/7,459 (1.7%); RR 0.70 (95% CI 0.50-0.99); nonfatal CVD events - 39/864 (4.5%); RR 0.85 (95% CI 0.46-1.58).

Fatal and non-fatal stroke events (Analysis 2.8, Analysis 2.9 and Analysis 2.10)

Seven trials with 21,556 participants reported on combined fatal and non-fatal stroke events. Only one trial was stopped prematurely was able to demonstrate a significant reduction in this combined outcome with the use of statins. The significant reduction was maintained in the pooled analysis using a fixed effects model: 450 (2.1%) events; RR 0.78 (95% CI 0.65-0.94) Only one trial with 6,595 participants reported on fatal stroke events and an-

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other one with 255 participants on non-fatal stroke events. No significant risk reduction was seen for these endpoints; fatal stroke events - 10/6595 (0.2%); RR 1.50 (95% CI 0.42-5.30) and non-fatal stroke events, 1/255 (0.4); RR 2.98 (95%CI 0.12-72.39).

Combined fatal and non-fatal CHD, CVD and stroke events (Analysis 2.11)

Only three trials with 17,452 participants reported a composite of fatal and non-fatal events for CHD, CVD and stroke. All three of the trials showed a significant reduction in this composite outcome with the treatment of statins which was maintained in the pooled analysis and using a fixed model: 938 (5.4%) events; RR 0.70 (95% CI 0.61-0.79)

Revascularisation (Analysis 1.4)

Five trials with 18,173 participants reported on the need for revascularisation procedures during follow-up: 313 (1.7%) underwent either PTCA or CABG. Two of the larger trials were able to demonstrate fewer revascularisation events in the intervention groups compared with the control groups with the use of statins and this was maintained in the pooled analysis using a fixed effects model were the a significant RR 0.66 (95% CI 0.53-0.83) was observed.

Cholesterol (Analysis 3.1 and Analysis 3.2)

Nine trials with 11 arms provided data on total and 11 with 13 trial arms on LDL cholesterol. Observations are based on 15,357and 22,413 participants respectively. For both endpoints all trials were able to demonstrate significant reductions; total cholesterol a net difference -0.89 mmol/L (95% CI -1.20 to -0.57 mmol/L) and LDL cholesterol a net difference of -0.92 (95% CI -1.10 to -0.74 mmol/L). There was marked heterogeneity of effects in both analysis (I^2= 99%). It is likely that the heterogeneity is due to differences in the statin and dosage used- for example the dose of pravastatin ranged from10mg to 40mg in different trials. It is also possible that cholesterol outcomes were subject to reporting biases in some trials which might exaggerate the findings.

Adverse events figures (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17 and Analysis 1.18)

Seven trials (eight trial arms) provided data on the following adverse events: myalgia (muscle pain), rhabdomyolysis, cancer, lymphoma and melanoma. We also looked for data on changes in muscle and liver enzyme, aspartate and alanine aminotransferase. In total 3,385/19,555 (17.3%) participants experienced an adverse event. Pooling the events rates indicated no difference between the intervention and control groups with the use of statin using a fixed effects model: RR 0.99 (95% 0.94-1.05) (Analysis 1.1). No difference was also observed with the number of participants stopping statin treatment due to adverse events, however there was significant heterogeneity observed and a random effect model had to be applied (Analysis 1.2).

Cancer: 793/17,277 (4.5%) participants in six trials developed cancer (Analysis 1.5). No statistical differences were observed between the overall rates for cancer in the intervention and control groups nor in the subgroup analysis for individual cancers: prostrate, colon, lung, bladder, breast, gastro-intestinal, genitor-urinary tract, respiratory tract. No significant heterogeneity was observed in any of these comparisons. It is important to note that the subgroups analysis are confined to only two trials (AFCAPS/TexCAPS 1998 and WOSCOPS 1997) which provided these data.

The event rates for other adverse effects including lymphoma, melanoma, myalgia, or rhabdomyolysis was low and ranged from 0.03% (rhabdomyolysis) to 7.4% (myalgia). No differences between groups were observed. No significant heterogeneity was observed in any of these comparisons of the five trials which reported on these events.

None of the trials reported on changes in muscle enzymes, aspartate nor alanine aminotransferase. Two large trials reported that 4.4% (31/7031) of participants experienced changes in liver enzymes but the differences between the intervention and control groups were of no statistical significance. There was no significant heterogeneity.

Costs

One trial reported on costs. WOSCOPS which recruited men with hypercholesterolaemia found that the use of statin yielded substantial health benefits at a cost which was not prohibitive: an undiscounted gain of 2,460 years of life at a cost of £8,121 per life year gained.

Patient quality of life

There were no reliable data on patient quality of life. Cell A+B provided limited data suggesting that the intervention of lifestyle advise plus pravastatin reduced stress and sleeping problems.

Subgroups analysis

We intended do undertake subgroups analysis for gender, age, and extent of hyperlipidaemia. However, none reported these breakdowns. No statistical differences in outcomes were observed in age and sex.

Sensitivity analysis

We were unable to locate any unpublished studies. We, therefore, confined our sensitivity analysis to study quality and to study size. Study quality; since most of the trials used double blinding techniques and intention to treat analysis and were free from selection bias, we focused our attention on methods of randomisation. We were unable to determine the method of randomisation for four trials: Japanese MEGA, AFCAPS/TexCAPS; Aspen and HYRIM. Sensitivity analysis indicated no change in the overall results due method of randomisation used (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6; Analysis 5.7).

Study size: we confined our analysis to comparing large (>1000 participants) with small (<1000 participants) trials. Similarly, sensitivity analysis did not alter the overall results (Analysis 5.8; Analysis 5.9; Analysis 5.10; Analysis 5.11; Analysis 5.12; Analysis 5.13; Analysis 5.14).

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DISCUSSION

The trials included in this systematic review showed reductions in all-cause mortality, composite endpoints and revascularisations. These findings were associated with falls in blood cholesterol and LDL cholesterol in all trials reporting these outcomes but no excess of combined adverse events, cancers or specific biochemical markers were found. Trials tended not to report single end points of CHD or stroke events reflecting the small numbers of events and that they were powered for composite endpoints. There was limited evidence to suggest that the use of statins for primary prevention may be cost effective and improve patient perceived quality of life. Sensitivity analysis suggested that age of participants or size of trial did not alter the overall results.

Unlike previous reviews, we attempted to examine the effects of statins in patients without evidence of existing cardiovascular diseases and we attempted to examine specific outcomes rather than composite outcomes. Although the trials intended to recruit only people without evidence of CVD some trials did enter some with participants with CVD . Rather than exclude such trials we set an arbitrary threshold of 10% to avoid any major influence of effects of treatment on those with existing CVD. Whilst our results concur with some of the published data, our findings differ from others. Specifically we concur with the results on all cause mortality and adverse events in previous systematic reviews (Brugts 2009; Ebrahim 1999; Mills 2008; NICE 2006). However, most of the previous systematic reviews included trials where more than 10% had a previous history of CVD. In two recently published reviews the baseline all-cause mortality event rates were 1.4 per 100 person years at risk (Mills 2008) and 1.7 per 100 person years (Brugts 2009) compared with 1.0 per 100 person years in this review. These findings suggest that these recent reviews have tended to select trials including sicker people than those included in our review which aimed to target only trials of primary prevention. Consequently, it is not surprising that findings for specific outcomes - rather than composite outcomes - differ between reviews. For example our review and one previous review (Thavendiranathan2006) did not find strong evidence of any reduction in CHD mortality whereas in a review where up to 50% of participants had suffered prior CVD, a 54% reduction in CHD mortality was reported (Mills 2008) - reflecting the strong evidence that statins are beneficial in secondary prevention. A major individual patient data meta-analysis - the Cholesterol Treatment Trialists' Collaboration - of 14 trials including over 90,000 participants reported sub-group findings in people without prior evidence of myocardial infarction or other coronary heart disease and found large reductions in major vascular endpoints (treated rate 8.5% vs. control rate10.6%; RR 0.78, 99% CIs 0.72 to 0.84) and major coronary events (treated rate 4.5% vs. control rate 6.1%; RR 0.72, 99% CIs 0.66, 0.80) that were near identical to findings in people with prior CVD (Baigent 2005). These findings have been criticized on the grounds that the CTT collaborators did not disaggregate the primary and secondary prevention findings but report on a group with "no MI or other CHD" at baseline which includes a substantial number of people with pre-existing stroke, peripheral vascular disease and diabetes which would have inflated the finding for absolute risk reduction (Abramson 2007). The CTT collaborators have not been able to provide the relevant analyses for inclusion in our review.

It is important to remain cautious in interpreting our results for combined end-points. In the majority of trials, power calculations were based on composite outcomes and not on single outcomes. Despite efforts to minimize bias in terms of blinding and use of intention to treat analysis, over one third of trials reported outcomes selectively. Eight trials did not report on adverse events at all. Moreover, the majority of trials focused their attention on different combinations of outcomes to ascertain a composite outcome. It was not always possible to ascertain or decipher these i.e. whether an individual who had a non-fatal clinical event followed by a fatal clinical event was counted as a clinical event under both categories. As a result, much useful data for this systematic review was lost. For example, the Japanese MEGA trials (whose study populations account of 24% of the total) provided data on combined fatal and non-fatal CHD events but not on fatal CHD events and non-fatal CHD events separately.

Furthermore, two of the larger trials were prematurely stopped because significant reductions in primary composite outcomes had been observed. This was also the case with the recently published JUPITER trial of rosuvastatin in people with raised C-reactive protein (JUPITER 2008) where the benefits of the reductions seen in a composite outcome of major cardiovascular events and specific endpoints at two years into the trial were considered sufficient to stop the trial. Nearly half the participants in the JUPITER trial suffered with metabolic syndrome and the baseline all-cause mortality rate in the control group was 1.25 per 100 patient years, 25% higher than in our systematic review. Early stopping of trials is of particular concern because in this and other situations early stopping may lead to an over-estimation of treatment effects particularly when the number of events is small. (Bassler 2007; Hlatky 2008; Montori 2005)

Caution also needs to be taken regarding the fact that all but one of the trials had some form of pharmaceutical industry sponsorship. It is now established that published pharmaceutical industry-sponsored trials are more likely than non-industry-sponsored trials to report results and conclusions that favour drug over placebo due to biased reporting and/or interpretation of trial results (Als-Nielsen 2003). In primary prevention where world-wide the numbers of patients eligible for treatment are massive, there might be motivations to use composite outcomes and early stopping to get results that clearly support intervention.

Overall the populations sampled within this review were white, male and middle aged. Therefore, caution needs to be taken regarding generalisability to older people who may be at greater risk

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of side effects and to women who are at lower risk of CVD events. Potential hazards of statins have been highlighted is small studies and some, such as increased risk of cancers, can be discounted by the evidence from the trials. However, even the more recent trials have not assessed potentially important side effects (e.g. possible cognitive impairments suggested by a small trial: Muldoon 2000) or have played down real increases in risk of diabetes with intensive cholesterol lowering (JUPITER 2008).

Two major trials were excluded from this review because of our criterion of only including trials with fewer than 10% of participants having a prior CVD diagnosis. ALLHAT-LLT (ALLHAT-LLT 2002) randomised 14% participants with a history of CHD (other CVD diagnoses were not reported) and ASCOT-LLA (ASCOT-LLA 2003) randomised 18% participants with a history of stroke or TIA, peripheral vascular disease or other cardiovascular diseases. As these trials were predominantly of primary prevention, their findings are of some relevance to the question of primary prevention despite not fulfilling our criteria. ALLHAT-LLT did not find any strong evidence of a reduction in all-cause mortality (RR 0.99; 95% CI: 0.89 to 1.11) or in CHD deaths (RR 0.99; 95% CI: 0.84 to 1.16) in those randomised to pravastatin compared to usual care. ASCOT-LLA, which randomised participants to atorvastatin or placebo, also found no strong evidence of a reduction in all-cause mortality (RR 0.87; 95% CI: 0.71 to 1.06) or in CVD mortality (RR 0.90; 95% CI: 0.66 to 1.23) despite achieving much greater cholesterol lowering effects than observed in ALLHAT-LLA. Combining evidence from these two trials with the estimates made in this review, the effects for all-cause mortality attenuate to RR 0.91; 95% CI: 0.84 to 0.99 and for CVD mortality to RR 0.92; 95% CI: 0.81 to 1.05.

In an update to a previous review claiming that statins gave no overall benefit in primary prevention (Therapeutics Letter 2003), the effects on all-cause mortality in trials of statins for primary prevention were RR 0.93, 95% CI: 0.86 to 1.00 and this attenuated to RR 0.99, 95% CI: 0.90 to 1.08 when four trials with serious risks of bias were excluded in a sensitivity analysis (Therapeutics Letter 2010). On the basis of these findings and a recent meta-analysis that managed to obtain data solely on patients without prior CVD diagnoses from four large trials (ALLHAT-LLT 2002; ASCOT-LLA 2003; PROSPER 2002; WOSCOPS 1997) and reported a total mortality of RR 0.93, 95% CI: 0.86 to 1.00) (Ray 2010), it was concluded that any apparent mortality or net health benefit of statins for primary prevention is more likely from trials where various biases may have arisen rather than a real effect (Therapeutics Letter 2010).

On the basis of our systematic review and these recent meta-analyses, it is clear that any decision to use statins for primary prevention should be made cautiously and in the light of an assessment of the patient's overall cardiovascular risk profile. Widespread use of statins in people at low risk of cardiovascular events - below a 1% annual all-cause mortality risk or an annual CVD event rate of below 2% observed in the control groups in the trials considered here - is not supported by the existing evidence. Furthermore, the tendency of trial protocols to remove patients suffering with co-morbidities limits their generalisability to typical patient populations in whom decisions to prescribe statins have to made.

Our review is not able to comment on cost-effectiveness as, surprisingly, few of the trials have published cost-effectiveness data to support their contentions that these drugs are worth using for primary prevention. Cost effectiveness analysis are price sensitive and need to be reviewed in the light of changes in cost and changes in prescribing (Ward 2007). Due to the assumed benefits of statin therapy in secondary prevention trials, and the recent systematic reviews (Baigent 2005; Brugts 2009; Mills 2008) concluding that statin prescribing may improve survival and be of benefit in the prevention CVD in people without cardiovascular disease, the need for cost effectiveness analyses may be viewed as unnecessary. However, commentary on the JUPITER trial makes it clear that decisions to treat ever more people with statins depends on a careful appraisal of the balance of benefits to safety and costs (Hlatky 2008). As noted by commentators, JUPITER demonstrated that treating 120 people for 1.9 years with rosuvastatin (at a cost of about US$287,000) would prevent one cardiovascular event (http://blogs.nature.com/mfenner/2008/11/23/what-are-the-right-numbers-for-jupiter; accessed 10 October 2010).

National Institute for Health & Clinical Excellence UK (NICE) has provided some estimates based on data to 2005 and conclude that an annual risk of a CHD event ranging from 3% to 0.5%, the ranges of cost per quality adjusted life year gained (QALY) gained were £10,000 to £31,000 at age 45 years, £13,000 to £40,000 at age 55 years using older generic statins (NICE 2006). Their guidance is to use statins "... as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD." Evidence supporting the use of statins as part of an overall strategy of identification of people at high risk of CVD events and lowering blood pressure and blood cholesterol has been produced for low and middle income countries (Lim 2007) and is now part of World Health Organisation policy for CVD prevention (WHO 2008b).

AUTHORS' CONCLUSIONS

Implications for practice

This current systematic review highlights the shortcomings in the published trials of statins for primary prevention. Selective reporting and inclusion of people with cardiovascular disease in many of the trials included in previous reviews of their role in primary prevention make the evidence impossible to disentangle without individual patient data. In people at high risk of cardiovascular events due to their risk factor profile (i.e. 20+% 10-year risk), it is likely that the benefits of statins are greater than potential short

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term harms although long-term effects (over decades) remain unknown. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

Implications for research

As newer statins are developed it is likely that further trials will be conducted in lower risk populations to extend the evidence base particularly among younger people with adverse risk factor profiles which are associated with higher life time CVD risk (Berry 2009). It is important that these trials examine potential adverse effects of statins and report on them in an unbiased way. Use of composite outcomes is reasonable given the small number of events arising among low risk populations but disaggregation of events by cause is helpful for better understanding of the effects of statins and for future systematic reviews of trials. More attention should be given to studying possible cognitive impairment associated with use of statins. Individual patient data meta-analyses have provided an initial appraisal of the evidence available to 2004. Further updates focusing on effects of statins among people without pre-existing disease and for a range of predicted CVD risk would help clarify the role of statins in primary prevention.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACAPS 1994

Methods	Randomised trial 4x4 factorial	
Participants	919 participants based in the USA aged 40 - 79 (mean age of 62); 52% male	
Interventions	20mg lovastatin + 1mg warfarin versus placebo followed up for 34 months	
Outcomes	Carotid atherosclerosis, cholesterol, fatal + non-fatal CHD events, stroke	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Blocked randomisation stratified by centre
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Carers and patients were blinded
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Adult Japanese MEGA Study

Methods	Randomised trial
Participants	8009 participants with hypercholesterolaemia based in Japan aged 40-70 (mean age 59) ; 32% male
Interventions	10-20mg pravastatin versus placebo; all participants got advice on diet; follow-up 5 years
Outcomes	Primary: composite of major CVD events, sudden cardiac death, angina and revascularisation. Single outcomes included: all cause mortality, total CVD events, fatal and non-fatal MI, stroke and TIA events, sudden cardiac death, angina and revascularisation, cholesterol, adverse events.
Notes	
Risk of bias	

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Adult Japanese MEGA Study (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	No	open label for patients since placebo-controlled trials in Japan are regarded with suspicion
Incomplete outcome data addressed? All outcomes	Unclear	Not described
Free of selective reporting?	Yes	other than adverse events in detail

AFCAPS/TexCAPS 1998

Methods	Randomised trial
Participants	6606 participants in Texas, USA; mean age 58; 57.5% male; 89% Caucasian
Interventions	20-40 mg lovastatin compared with placebo; follow-up for 5.2 years; all participants received advice on diet
Outcomes	Primary: composite of fatal and nonfatal MI and fatal CHD events. Single outcomes included: all cause mortality, fatal and non-fatal CVD + stroke events, heart failure and adverse events.
Notes	Trial was stopped prematurely. To be terminated when 320 participants had experienced primary outcome event. Stopped when 267 had done so.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	double blind-participants and personnel
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	other than results for cholesterol

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ASPEN 2006

Methods	Randomised trial	
Participants	2,410 participants with type 2 diabetes based in 16 developed countries with mean age 60; 62.5% male; 84% Caucasian	
Interventions	10mg atorvastatin versus placebo; follow-up of 2.4 years (for primary prevention participants)	
Outcomes	Primary: composite of fatal MI, stroke, sudden cardiac death, heart failure, CVD death. Single outcomes included: non-fatal or silent MI + stroke, revascularisation, resuscitated cardiac arrest, TIA, unstable angina, peripheral arterial disease, Ischaemic heart failure and adverse events.	
Notes	Primary prevention participants recruited 2-3 years into the study	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	double-blind: participants and outcome assessors
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	other than not providing results on adverse events for primary prevention group

CAIUS 1996

Methods	Randomised trial	
Participants	305 participants with hypercholesterolaemia based in Italy with mean age 55; 53% male	
Interventions	40mg pravastatin versus placebo; follow-up of three years	
Outcomes	Slope of carotid artery, fatal and nonfatal MI, angina, revascularisations, cholesterol and adverse events.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

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CAIUS 1996 (*Continued*)

Adequate sequence generation?	Yes	Independent co-ordinating centre controlled allocation
Allocation concealment?	Yes	Independent co-ordinating centre controlled allocation
Blinding? All outcomes	Unclear	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	

CARDS 2004

Methods	Randomised control trial
Participants	2838 participants with diabetes based in UK and Ireland aged 40-75 years (mean 61.7) ; 68% male; 94.5% Caucasian
Interventions	10mg atorvastatin, all patients were given counselling on cessation of smoking; follow up of 3.9-4 years
Outcomes	Primary: composite of fatal and nonfatal MI, acute CHD death, resuscitated cardiac arrest. Single outcomes included: all cause mortality, fatal and non-fatal or silent MI + stroke, revascularisation, resuscitated cardiac arrest, total CVD events, adverse events and cholesterol.
Notes	Trial stopped prematurely due to large beneficial treatment effect

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	computer generated randomisation code
Allocation concealment?	Yes	Staff and patients unaware of computer generated randomisation code
Blinding? All outcomes	Yes	triple-blind: participants, personnel and outcome assessors
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	

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CELL A 1996

Methods	Randomised trial; 2x3 factorial design	
Participants	228 participants with hyperlipidaemia based in Sweden with a mean age of 49; 85% male	
Interventions	10-40mg pravastatin plus intensive dietary advice versus placebo; follow-up for 18 months	
Outcomes	Fatal MI, cholesterol, quality of life.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Not described
Allocation concealment?	Yes	Randomisation performed separately for each centre with numbers allocated to intervention and control groups
Blinding? All outcomes	Yes	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	No	adverse events rates not provided for each group

CELL B 1996

Methods	Randomised trial; 2x3 factorial design	
Participants	227 participants with hyperlipidaemia based in Sweden with a mean age of 49; 85% male	
Interventions	10-40mg pravastatin plus dietary advice versus placebo; follow-up for 18 months	
Outcomes	Fatal MI, cholesterol, quality of life.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

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CELL B 1996 (*Continued*)

Adequate sequence generation?	Yes	Not described
Allocation concealment?	Yes	Randomisation performed separately for each centre with numbers allocated to intervention and control groups
Blinding? All outcomes	Yes	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Unclear	CVD and adverse events rates not provided for each group

Derosa 2003

Methods	Randomised trial
Participants	47 participants with hypercholesterolaemia based in Italy with a mean age of 51; 46% male
Interventions	80mg fluvastatin versus placebo; all participants were given advice on diet and exercise ; follow-up for one year
Outcomes	Adverse events, cholesterol.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Envelopes containing randomisation codes prepared by statistician
Allocation concealment?	Yes	Allocation code could only be identified by statistician and person responsible for statistical analysis
Blinding? All outcomes	Yes	single blind: participants
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	

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HYRIM 2004

Methods	Randomised trial 2x2 factorial design	
Participants	287 men with hypertension based in Norway aged 40-75 years (mean age 57)	
Interventions	40mg fluvastatin; follow up four years	
Outcomes	Primary: composite of fatal and nonfatal MI, + stroke, angina, sudden CHD death, TIA and heart failure. MACE: composite of cardiac death, fatal and nonfatal MI and revascularisation. Single outcomes included: adverse events, cholesterol.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	Unclear	Not described
Free of selective reporting?	Yes	mostly but not for adverse events and cholesterol level at baseline and at 4 year follow-up not provided

KAPS 1995

Methods	Randomised trial	
Participants	447 men based in Finland aged 44-65 years (mean 57)	
Interventions	40mg pravastatin versus placebo; follow-up of 3 years	
Outcomes	Carotid atherosclerotic progression, total mortality, fatal and non-fatal MI events, stroke, adverse events, cholesterol, other cardiac death, revascularisations, non cardiac death and heart failure.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

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KAPS 1995 (*Continued*)

Adequate sequence generation?	Yes	Biostatistician prepared randomisation scheme-
Allocation concealment?	Yes	Tablets were masked by pharmaceutical company
Blinding? All outcomes	Yes	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	No	17% patients dropped out and were excluded from the analysis
Free of selective reporting?	Yes	

MRC/BHF Heart Protection

Methods	randomised trial (2x2 factorial design)
Participants	3982 patients with no prior CHD with diabetes mellitus as a subset of 20,536 UK adults aged 40-80 years
Interventions	40mg simvastatin compared with placebo, follow up 5.3 years for all participants
Outcomes	Composite of coronary and vascular events, stroke, revascularisations
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Not described
Allocation concealment?	Yes	Central telephone system used
Blinding? All outcomes	Yes	double blind: participants and outcome assessors
Incomplete outcome data addressed? All outcomes	Unclear	Not described
Free of selective reporting?	No	only CVD event results provided for this subgroup

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PHYLLIS A 2004

Methods	Randomised trial 4x4 factorial	
Participants	253 men and women aged 45-70 (mean age 58) with hypertension, hypercholesterolaemia and asymptomatic carotid atherosclerosis based in Italy	
Interventions	25 mg hydrochlorothiazide + 40 mg pravastatin followed up for 2.6 years	
Outcomes	Primary outcomes: carotid atherosclerosis. Secondary outcomes: non-fatal MI, CVD death, stroke, cholesterol and cancer	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation was computer generate in blocks of 4
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

PHYLLIS B 2004

Methods	Randomised trial 4x4 factorial	
Participants	255 men and women aged 45-70 (mean age 58) with hypertension, hypercholesterolaemia and asymptomatic carotid atherosclerosis based in Italy	
Interventions	20 mg fosinopril + 40 mg pravastatin followed up for 2.6 years	
Outcomes	Primary outcomes: carotid atherosclerosis. Secondary outcomes: non-fatal MI, CVD death, stroke, cholesterol and cancer	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation was computer generate in blocks of four.

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PHYLLIS B 2004 (*Continued*)

Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

PREVEND IT 2004

Methods	Randomised trial 2x2 factorial design
Participants	864 participants with microalbuminuria based in Holland aged 28-75 years (mean age 51); 64.5% male; 96% Caucasian
Interventions	40mg pravastatin versus placebo; follow-up 3.8 years
Outcomes	Primary outcome: composite of fatal and non-fatal CVD events. Single outcomes included fatal CVD events, stroke, heart failure, nonfatal MI and cholesterol.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation was computer generated.
Allocation concealment?	Yes	Subjects randomised were allocated to a treatment number.
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	No	Intention to treat analysis confined to CVD events, 6% dropped out
Free of selective reporting?	Yes	

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WOSCOPS 1997

Methods	Randomised trial	
Participants	6595 men with hypercholesterolaemia based in Scotland aged 45-64 (mean age 55)	
Interventions	40mg pravastatin versus placebo; follow-up 4.9 years	
Outcomes	Primary outcome: composite of non-fatal MI and CHD death. Single outcomes included total mortality, fatal CVD events, cholesterol, revascularisations, non-fatal MI and CHD death and adverse events.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Not described
Allocation concealment?	Yes	All trial personnel remained unaware of the subject's treatment assignment throughout the study.
Blinding? All outcomes	Yes	double-blind: participants and personnel
Incomplete outcome data addressed? All outcomes	Yes	Intention to treat analysis used
Free of selective reporting?	Yes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ALLHAT-LLT 2002	15% patients had history of CVD
Anderson 1993	No Placebo - Statin + antioxidant versus Statin + antioxidant
ASCOT-LLA 2003	18% patients had history of CVD
Bak 1998	Treatment length was only 6 months
BCAPS 2001	11% had history of CVD
Boccuzzi 1991	Not an RCT - all participants were given Simvastatin
Branchi	Control Group was not randomised

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(*Continued*)

Cassader 1993	Treatment length was only 24 weeks
Chan 1996	Treatment length is only nine months
CLIP 2002	Not an RCT - All participants were given Pravastatin
CRISP 1994	Treatment length is only 48 weeks
CURVES 1998	No Placebo - Statin Versus Statin
Dangas 1999	Treatment length is only six months
Davidson 1997	No Placebo - Statin Versus Statin
Duffy 2001	Treatment length is only six months
Egashira 1994	Not an RCT - All participants were given Pravastatin
Eriksson 1998	No control group - Pravastatin vs. Cholestyramine
EXCEL 1990	Treatment length was only 48 weeks
FAST 2002	Over 40% had CVD and over 14% had CHD
Ferrari 1993	Treatment length is only 26 weeks
Gentile 2000	Treatment length was only 24 weeks
Glasser 1996	Length of treatment is only 12 weeks
Hokuriku NK-104 Study	Not an RCT - All participants were given intravasating
Hufnagel 2000	Treatment length is only four months
Italian Family Physician	Not an RCT - open labelled
Jardine 2006	Outcomes provided were aggregated. Unable to ascertain actual numbers for cardiac death and myocardial infarction.
Jones 1991	Length of treatment is only eight weeks
KLIS 2000	Not randomised
Lemaitre 2002	Cohort study
McGrae McDremott 2003	Subjects were not randomised to statins or no statins

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(*Continued*)

Mohler 2003	Patients recruited had peripheral arterial disease
Muldoon 1997	Treatment length is only six months
Nephrotic Syndrome Study	Treatment length was only nine months
Ohta 2000	Treatment length is only six months
Oi 1997	No placebo or control group
Ormiston 2003	Not an RCT - all participants were given statins
Pitt 1999	No Placebo - Statins versus Angioplasty
POSCH 1990	Statins were not used
Pravastatin Multi 1993	Treatment length was only 26 weeks
PROSPER 2002	More than 10% of the participants had CVD
Sprecher 1994	Treatment length is only 24 weeks
Stein 1997	Treatment length is only four weeks
Su 2000	Treatment length is only six months
Tanaka 2001	Treatment length is only 12 weeks
Thomas 1993	Treatment length is only 24 weeks
Thrombosis Prevention	Statins were not used
Wallace 2003	Treatment length was only 8 weeks
Yu-An 1998	Treatment length was less than one year

Characteristics of studies awaiting assessment *[ordered by study ID]*

JUPITER 2008

Methods	Randomised trial
Participants	17,802 participants >50 years without history of CVD
Interventions	Rosuvastatin 20 mg daily

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JUPITER 2008 (*Continued*)

Outcomes	All cause mortality, fatal and non fatal CVD events, revascularisation
Notes	Stopped prematurely

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DATA AND ANALYSES

Comparison 1. Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of study participants that had Adverse Events	8	19555	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.94, 1.05]
2 Number of Study Participants that Stopped Treatment Due to Adverse Events	5	17328	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.10]
3 Number of Study Participants that were admitted to Hospital	1	1905	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.45]
4 Number of Study Participants underwent revascularisation	5	18173	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.53, 0.83]
5 Number of Study Participants who developed cancer	7	17277	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.12]
6 Number of Study Participants who develop Myalgia or muscle pain	4	16464	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.14]
7 Number of Study Participants who develop Rhabdomyolysis	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
8 Number of Study Participants who had elevated Liver Enzymes	2	7031	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.77, 3.25]
9 Number of Study Participants that developed Prostate Cancer	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.31]
10 Number of Study Participants who developed Melanoma	2	13200	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.48]
11 Number of Study Participants who developed Colon Cancer	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.70, 2.24]
12 Number of Study Participants who developed Lung Cancer	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.69, 2.43]
13 Number of Study Participants who develop Lymphoma	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.48, 2.47]
14 Number of Study Participants who develop Bladder Cancer	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.48, 2.47]
15 Number of Study Participants who develop Breast Cancer	1	6605	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.62, 3.37]
16 Number who developed Gastro-intestinal Cancers	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.73, 2.05]
17 Number of Study Participants who developed Genito-urinary tract Cancers	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.57, 1.63]
18 Number who developed Respiratory Tract Cancers	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.67, 2.08]

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Comparison 2. Mortality and Morbidity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Mortality	8	28161	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
2 Number of Fatal CHD Events	7	17619	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.59, 1.04]
3 Number of Non-fatal CHD Events	7	4927	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.50, 1.10]
4 Total Number of CHD Events	10	27969	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.79]
5 Number of Fatal CVD Events	2	7459	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
6 Number of Non-fatal CVD Events	1	864	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.46, 1.58]
7 Total Number of CVD Events	6	12286	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.66, 0.85]
8 Number of Fatal Stroke Events	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.30]
9 Number of Non-fatal Stroke Events	1	255	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.12, 72.39]
10 Total Number of Stroke Events	7	21556	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.65, 0.94]
11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events	3	17452	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.79]

Comparison 3. Lipids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Cholesterol	11	15357	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.20, -0.57]
2 LDL Cholesterol	13	22413	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.10, -0.74]

Comparison 4. Treatment Compliance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment Compliance	4	14490	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.99, 1.14]

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Comparison 5. Sensitivity Analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Randomisation for Total Mortality	7	27242	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.97]
1.1 Randomisation method known	4	10723	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.65, 0.95]
1.2 Randomisation method not known	3	16519	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
2 Randomisation for Fatal CHD Events	6	16700	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.08]
2.1 Randomisation method known	4	8190	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.50, 1.02]
2.2 Randomisation method not known	2	8510	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.64, 1.63]
3 Randomisation for Non-fatal CHD Events	4	3500	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.14]
3.1 Randomisation method known	3	1595	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.30, 1.12]
3.2 Randomisation method not known	1	1905	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.63]
4 Randomisation for Fatal CVD Events	2	7459	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
4.1 Randomisation method known	2	7459	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
5 Randomisation for Non-fatal CVD Events	1	864	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.46, 1.58]
5.1 Randomisation method known	1	864	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.46, 1.58]
6 Randomisation for Fatal Stroke Events	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.30]
6.1 Randomisation method known	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.30]
7 Randomisation for total number of fatal and non-fatal CHD, CVD and Stroke Events	3	17359	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.61, 0.78]
7.1 Randomisation method known	1	2838	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.57, 0.86]
7.2 Randomisation method not known	2	14521	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.80]
8 Study Size for Total Mortality	7	27242	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.97]
8.1 Over 1000 participants	5	25952	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
8.2 Under 1000 participants	2	1290	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.51, 2.26]
9 Study Size for Fatal CHD Events	6	16700	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.08]
9.1 Over 1000 participants	3	15105	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.62, 1.15]
9.2 Under 1000 participants	3	1595	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.33, 1.37]
10 Study Size for Non-fatal CHD Events	4	3500	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.14]

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10.1 Over 1000 participants	1	1905	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.63]
10.2 Under 1000 participants	3	1595	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.30, 1.12]
11 Study Size for Fatal CVD Events	2	7459	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.99]
11.1 Over 1000 participants	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.98]
11.2 Under 1000 participants	1	864	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 3.95]
12 Study Size for Non-fatal CVD Events	1	864	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.46, 1.58]
12.1 Under 1000 participants	1	864	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.46, 1.58]
13 Study Size for Fatal Stroke Events	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.30]
13.1 Over 1000 participants	1	6595	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.30]
14 Study Size for total number of fatal and non-fatal CHD, CVD and stroke events	3	17452	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.79]
14.1 Over 1000 participants	3	17452	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.79]

Analysis 1.1. Comparison 1 Adverse Events, Outcome 1 Number of study participants that had Adverse Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 1 Number of study participants that had Adverse Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adult Japanese MEGA Study	396/3958	425/4051		24.7 %	0.95 [0.84, 1.09]
AFCAPS/TexCAPS 1998	1131/3304	1126/3301		66.3 %	1.00 [0.94, 1.07]
CAIUS 1996	15/151	14/154		0.8 %	1.09 [0.55, 2.18]
CARDS 2004	19/1428	20/1410		1.2 %	0.94 [0.50, 1.75]
KAPS 1995	107/214	95/212		5.6 %	1.12 [0.91, 1.36]
PHYLLIS A 2004	1/126	0/127		0.0 %	3.02 [0.12, 73.53]
PHYLLIS B 2004	0/128	1/127		0.1 %	0.33 [0.01, 8.04]
PREVEND IT 2004	13/433	22/431		1.3 %	0.59 [0.30, 1.15]
Total (95% CI)	**9742**	**9813**		**100.0 %**	**0.99 [0.94, 1.05]**

Total events: 1682 (Statin Therapy Group), 1703 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 5.14$, df = 7 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.27 (P = 0.78)

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Analysis 1.2. Comparison 1 Adverse Events, Outcome 2 Number of Study Participants that Stopped Treatment Due to Adverse Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 2 Number of Study Participants that Stopped Treatment Due to Adverse Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AFCAPS/TexCAPS 1998	449/3304	445/3301		36.1 %	1.01 [0.89, 1.14]
CARDS 2004	122/1428	145/1410		19.9 %	0.83 [0.66, 1.04]
KAPS 1995	8/214	12/212		2.1 %	0.66 [0.28, 1.58]
PREVEND IT 2004	23/433	33/431		5.6 %	0.69 [0.41, 1.16]
WOSCOPS 1997	471/3302	432/3293		36.2 %	1.09 [0.96, 1.23]
Total (95% CI)	**8681**	**8647**		**100.0 %**	**0.97 [0.85, 1.10]**

Total events: 1073 (Statin Therapy Group), 1067 (Usual Care or Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.15$, df = 4 (P = 0.13); $I^2 = 44\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Analysis 1.3. Comparison 1 Adverse Events, Outcome 3 Number of Study Participants that were admitted to Hospital.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

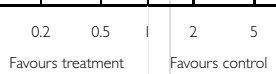
Outcome: 3 Number of Study Participants that were admitted to Hospital

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ASPEN 2006	65/959	62/946		100.0 %	1.03 [0.74, 1.45]
Total (95% CI)	**959**	**946**		**100.0 %**	**1.03 [0.74, 1.45]**

Total events: 65 (Statin Therapy Group), 62 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)



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Analysis 1.4. Comparison 1 Adverse Events, Outcome 4 Number of Study Participants underwent revascularisation.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 4 Number of Study Participants underwent revascularisation

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adult Japanese MEGA Study	42/3958	68/4051		35.6 %	0.63 [0.43, 0.93]
CAIUS 1996	3/151	2/154		1.1 %	1.53 [0.26, 9.03]
CARDS 2004	24/1428	34/1410		18.1 %	0.70 [0.42, 1.17]
KAPS 1995	4/214	5/212		2.7 %	0.79 [0.22, 2.91]
WOSCOPS 1997	51/3302	80/3293		42.5 %	0.64 [0.45, 0.90]
Total (95% CI)	**9053**	**9120**		**100.0 %**	**0.66 [0.53, 0.83]**

Total events: 124 (Statin Therapy Group), 189 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 1.07, df = 4 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 3.64 (P = 0.00028)

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Analysis 1.5. Comparison 1 Adverse Events, Outcome 5 Number of Study Participants who developed cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 5 Number of Study Participants who developed cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	252/3304	259/3301		64.3 %	0.97 [0.82, 1.15]
CAIUS 1996	3/151	4/154		1.0 %	0.76 [0.17, 3.36]
CARDS 2004	20/1428	30/1410		7.5 %	0.66 [0.38, 1.15]
KAPS 1995	0/214	1/212		0.4 %	0.33 [0.01, 8.06]
PHYLLIS A 2004	1/126	0/127		0.1 %	3.02 [0.12, 73.53]
PHYLLIS B 2004	0/128	1/127		0.4 %	0.33 [0.01, 8.04]
WOSCOPS 1997	116/3302	106/3293		26.3 %	1.09 [0.84, 1.41]
Total (95% CI)	**8653**	**8624**		**100.0 %**	**0.98 [0.85, 1.12]**

Total events: 392 (Statin Therapy Group), 401 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 4.08$, df = 6 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.36 (P = 0.72)

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Analysis 1.6. Comparison 1 Adverse Events, Outcome 6 Number of Study Participants who develop Myalgia or muscle pain.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 6 Number of Study Participants who develop Myalgia or muscle pain

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	11/3304	11/3301		4.5 %	1.00 [0.43, 2.30]
CARDS 2004	61/1428	72/1410		29.4 %	0.84 [0.60, 1.17]
KAPS 1995	48/214	42/212		17.1 %	1.13 [0.78, 1.64]
WOSCOPS 1997	117/3302	121/3293		49.1 %	0.96 [0.75, 1.24]
Total (95% CI)	**8248**	**8216**		**100.0 %**	**0.96 [0.81, 1.14]**

Total events: 237 (Statin Therapy Group), 246 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 1.44, df = 3 (P = 0.70); I^2 =0.0%

Test for overall effect: Z = 0.50 (P = 0.62)

Analysis 1.7. Comparison 1 Adverse Events, Outcome 7 Number of Study Participants who develop Rhabdomyolysis.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 7 Number of Study Participants who develop Rhabdomyolysis

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	1/3304	3/3301		100.0 %	0.33 [0.03, 3.20]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**0.33 [0.03, 3.20]**

Total events: 1 (Statin Therapy Group), 3 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.95 (P = 0.34)

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Analysis 1.8. Comparison 1 Adverse Events, Outcome 8 Number of Study Participants who had elevated Liver Enzymes.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 8 Number of Study Participants who had elevated Liver Enzymes

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	18/3304	11/3301		91.6 %	1.63 [0.77, 3.46]
KAPS 1995	1/214	1/212		8.4 %	0.99 [0.06, 15.74]
Total (95% CI)	**3518**	**3513**		**100.0 %**	**1.58 [0.77, 3.25]**

Total events: 19 (Statin Therapy Group), 12 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 1.24 (P = 0.21)

Analysis 1.9. Comparison 1 Adverse Events, Outcome 9 Number of Study Participants that developed Prostate Cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 9 Number of Study Participants that developed Prostate Cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	109/3304	108/3301		100.0 %	1.01 [0.78, 1.31]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.01 [0.78, 1.31]**

Total events: 109 (Statin Therapy Group), 108 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.06 (P = 0.95)

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Analysis 1.10. Comparison 1 Adverse Events, Outcome 10 Number of Study Participants who developed Melanoma.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 10 Number of Study Participants who developed Melanoma

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AFCAPS/TexCAPS 1998	14/3304	27/3301		45.5 %	0.52 [0.27, 0.99]
WOSCOPS 1997	31/3302	30/3293		54.5 %	1.03 [0.63, 1.70]
Total (95% CI)	**6606**	**6594**		**100.0 %**	**0.75 [0.39, 1.48]**

Total events: 45 (Statin Therapy Group), 57 (Usual Care or Placebo)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 2.74$, df = 1 (P = 0.10); $I^2 = 63\%$

Test for overall effect: Z = 0.83 (P = 0.41)

Analysis 1.11. Comparison 1 Adverse Events, Outcome 11 Number of Study Participants who developed Colon Cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 11 Number of Study Participants who developed Colon Cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	25/3304	20/3301		100.0 %	1.25 [0.70, 2.24]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.25 [0.70, 2.24]**

Total events: 25 (Statin Therapy Group), 20 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.74 (P = 0.46)

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Analysis 1.12. Comparison 1 Adverse Events, Outcome 12 Number of Study Participants who developed Lung Cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 12 Number of Study Participants who developed Lung Cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	22/3304	17/3301		100.0 %	1.29 [0.69, 2.43]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.29 [0.69, 2.43]**

Total events: 22 (Statin Therapy Group), 17 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.80 (P = 0.42)

Analysis 1.13. Comparison 1 Adverse Events, Outcome 13 Number of Study Participants who develop Lymphoma.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 13 Number of Study Participants who develop Lymphoma

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	12/3304	11/3301		100.0 %	1.09 [0.48, 2.47]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.09 [0.48, 2.47]**

Total events: 12 (Statin Therapy Group), 11 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.84)

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Analysis 1.14. Comparison 1 Adverse Events, Outcome 14 Number of Study Participants who develop Bladder Cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 14 Number of Study Participants who develop Bladder Cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	12/3304	11/3301		100.0 %	1.09 [0.48, 2.47]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.09 [0.48, 2.47]**

Total events: 12 (Statin Therapy Group), 11 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.84)

Analysis 1.15. Comparison 1 Adverse Events, Outcome 15 Number of Study Participants who develop Breast Cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 15 Number of Study Participants who develop Breast Cancer

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
AFCAPS/TexCAPS 1998	13/3304	9/3301		100.0 %	1.44 [0.62, 3.37]
Total (95% CI)	**3304**	**3301**		**100.0 %**	**1.44 [0.62, 3.37]**

Total events: 13 (Statin Therapy Group), 9 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.40)

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Analysis 1.16. Comparison 1 Adverse Events, Outcome 16 Number who developed Gastro-intestinal Cancers.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

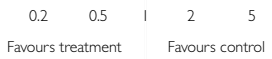
Outcome: 16 Number who developed Gastro-intestinal Cancers

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
WOSCOPS 1997	32/3302	26/3293		100.0 %	1.23 [0.73, 2.05]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**1.23 [0.73, 2.05]**

Total events: 32 (Statin Therapy Group), 26 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.78 (P = 0.44)



Analysis 1.17. Comparison 1 Adverse Events, Outcome 17 Number of Study Participants who developed Genito-urinary tract Cancers.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 17 Number of Study Participants who developed Genito-urinary tract Cancers

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
WOSCOPS 1997	27/3302	28/3293		100.0 %	0.96 [0.57, 1.63]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**0.96 [0.57, 1.63]**

Total events: 27 (Statin Therapy Group), 28 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.15 (P = 0.88)

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Analysis 1.18. Comparison 1 Adverse Events, Outcome 18 Number who developed Respiratory Tract Cancers.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Adverse Events

Outcome: 18 Number who developed Respiratory Tract Cancers

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
WOSCOPS 1997	26/3302	22/3293		100.0 %	1.18 [0.67, 2.08]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**1.18 [0.67, 2.08]**

Total events: 26 (Statin Therapy Group), 22 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

Analysis 2.1. Comparison 2 Mortality and Morbidity, Outcome 1 Total Mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 1 Total Mortality

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	0/460	4/459		1.0 %	0.11 [0.01, 2.05]
Adult Japanese MEGA Study	57/3958	81/4051		18.5 %	0.72 [0.51, 1.01]
AFCAPS/TexCAPS 1998	80/3304	77/3301		17.8 %	1.04 [0.76, 1.41]
ASPEN 2006	44/959	40/946		9.3 %	1.09 [0.71, 1.65]
CARDS 2004	61/1428	82/1410		19.1 %	0.73 [0.53, 1.01]
KAPS 1995	4/214	5/212		1.2 %	0.79 [0.22, 2.91]
PREVEND IT 2004	10/433	8/431		1.9 %	1.24 [0.50, 3.12]
WOSCOPS 1997	106/3302	135/3293		31.2 %	0.78 [0.61, 1.01]
Total (95% CI)	**14058**	**14103**		**100.0 %**	**0.84 [0.73, 0.96]**

Total events: 362 (Statin Therapy Group), 432 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 7.57, df = 7 (P = 0.37); I^2 =8%

Test for overall effect: Z = 2.53 (P = 0.011)

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Analysis 2.2. Comparison 2 Mortality and Morbidity, Outcome 2 Number of Fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

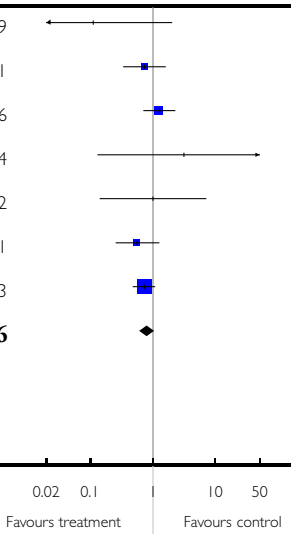
Outcome: 2 Number of Fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	0/460	4/459		4.1 %	0.11 [0.01, 2.05]
AFCAPS/TexCAPS 1998	11/3304	15/3301		13.7 %	0.73 [0.34, 1.59]
ASPEN 2006	24/959	19/946		17.5 %	1.25 [0.69, 2.26]
CAIUS 1996	1/151	0/154		0.5 %	3.06 [0.13, 74.51]
KAPS 1995	2/214	2/212		1.8 %	0.99 [0.14, 6.97]
PREVEND IT 2004	9/433	16/431		14.7 %	0.56 [0.25, 1.25]
WOSCOPS 1997	38/3302	52/3293		47.7 %	0.73 [0.48, 1.10]
Total (95% CI)	**8823**	**8796**		**100.0 %**	**0.78 [0.59, 1.04]**

Total events: 85 (Statin Therapy Group), 108 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 5.62$, df = 6 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 1.69 (P = 0.091)



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Analysis 2.3. Comparison 2 Mortality and Morbidity, Outcome 3 Number of Non-fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

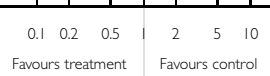
Outcome: 3 Number of Non-fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	5/460	5/459		9.1 %	1.00 [0.29, 3.42]
ASPEN 2006	20/959	22/946		40.1 %	0.90 [0.49, 1.63]
CAIUS 1996	2/151	2/154		3.6 %	1.02 [0.15, 7.15]
KAPS 1995	3/214	6/212		10.9 %	0.50 [0.13, 1.95]
PHYLLIS A 2004	0/126	3/127		6.3 %	0.14 [0.01, 2.76]
PHYLLIS B 2004	1/128	0/127		0.9 %	2.98 [0.12, 72.39]
PREVEND IT 2004	9/433	16/431		29.1 %	0.56 [0.25, 1.25]
Total (95% CI)	**2471**	**2456**		**100.0 %**	**0.74 [0.50, 1.10]**

Total events: 40 (Statin Therapy Group), 54 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 3.43, df = 6 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 1.47 (P = 0.14)



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Analysis 2.4. Comparison 2 Mortality and Morbidity, Outcome 4 Total Number of CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 4 Total Number of CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	5/460	9/459		1.0 %	0.55 [0.19, 1.64]
Adult Japanese MEGA Study	184/3958	280/4051		30.2 %	0.67 [0.56, 0.81]
AFCAPS/TexCAPS 1998	163/3304	215/3301		23.5 %	0.76 [0.62, 0.92]
ASPEN 2006	72/959	75/946		8.2 %	0.95 [0.69, 1.29]
CAIUS 1996	3/151	2/154		0.2 %	1.53 [0.26, 9.03]
CARDS 2004	51/1428	77/1410		8.4 %	0.65 [0.46, 0.92]
HYRIM 2004	6/142	9/143		1.0 %	0.67 [0.25, 1.84]
PHYLLIS A 2004	0/126	3/127		0.4 %	0.14 [0.01, 2.76]
PHYLLIS B 2004	1/128	0/127		0.1 %	2.98 [0.12, 72.39]
WOSCOPS 1997	174/3302	248/3293		27.1 %	0.70 [0.58, 0.84]
Total (95% CI)	**13958**	**14011**	◆	**100.0 %**	**0.72 [0.65, 0.79]**

Total events: 659 (Statin Therapy Group), 918 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 7.01$, df = 9 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 6.61 (P < 0.00001)

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Analysis 2.5. Comparison 2 Mortality and Morbidity, Outcome 5 Number of Fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 5 Number of Fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
PREVEND IT 2004	4/433	4/431		5.2 %	1.00 [0.25, 3.95]
WOSCOPS 1997	50/3302	73/3293		94.8 %	0.68 [0.48, 0.98]
Total (95% CI)	**3735**	**3724**		**100.0 %**	**0.70 [0.50, 0.99]**

Total events: 54 (Statin Therapy Group), 77 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 2.03 (P = 0.042)

Analysis 2.6. Comparison 2 Mortality and Morbidity, Outcome 6 Number of Non-fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 6 Number of Non-fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
PREVEND IT 2004	18/433	21/431		100.0 %	0.85 [0.46, 1.58]
Total (95% CI)	**433**	**431**		**100.0 %**	**0.85 [0.46, 1.58]**

Total events: 18 (Statin Therapy Group), 21 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)

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Analysis 2.7. Comparison 2 Mortality and Morbidity, Outcome 7 Total Number of CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 7 Total Number of CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CAIUS 1996	3/151	2/154		0.4 %	1.53 [0.26, 9.03]
HYRIM 2004	11/142	15/143		3.1 %	0.74 [0.35, 1.55]
MRC/BHF Heart Protection	276/2006	367/1976		76.2 %	0.74 [0.64, 0.85]
PHYLLIS B 2004	1/128	0/127		0.1 %	2.98 [0.12, 72.39]
PREVEND IT 2004	22/433	25/431		5.2 %	0.88 [0.50, 1.53]
WOSCOPS 1997	50/3302	73/3293		15.1 %	0.68 [0.48, 0.98]
Total (95% CI)	**6162**	**6124**		**100.0 %**	**0.74 [0.66, 0.85]**

Total events: 363 (Statin Therapy Group), 482 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 1.91$, df = 5 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 4.55 (P < 0.00001)

Analysis 2.8. Comparison 2 Mortality and Morbidity, Outcome 8 Number of Fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

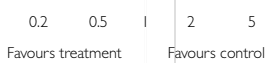
Outcome: 8 Number of Fatal Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
WOSCOPS 1997	6/3302	4/3293		100.0 %	1.50 [0.42, 5.30]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**1.50 [0.42, 5.30]**

Total events: 6 (Statin Therapy Group), 4 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)



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Analysis 2.9. Comparison 2 Mortality and Morbidity, Outcome 9 Number of Non-fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 9 Number of Non-fatal Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
PHYLLIS B 2004	1/128	0/127		100.0 %	2.98 [0.12, 72.39]
Total (95% CI)	**128**	**127**		**100.0 %**	**2.98 [0.12, 72.39]**

Total events: 1 (Statin Therapy Group), 0 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.67 (P = 0.50)

Analysis 2.10. Comparison 2 Mortality and Morbidity, Outcome 10 Total Number of Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

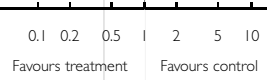
Outcome: 10 Total Number of Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	0/460	5/459		2.2 %	0.09 [0.01, 1.64]
Adult Japanese MEGA Study	94/3958	120/4051		46.9 %	0.80 [0.61, 1.05]
ASPEN 2006	27/959	29/946		11.6 %	0.92 [0.55, 1.54]
CARDS 2004	21/1428	39/1410		15.5 %	0.53 [0.31, 0.90]
KAPS 1995	2/214	5/212		2.0 %	0.40 [0.08, 2.02]
PREVEND IT 2004	7/433	4/431		1.6 %	1.74 [0.51, 5.91]
WOSCOPS 1997	46/3302	51/3293		20.2 %	0.90 [0.61, 1.34]
Total (95% CI)	**10754**	**10802**		**100.0 %**	**0.78 [0.65, 0.94]**

Total events: 197 (Statin Therapy Group), 253 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 7.40, df = 6 (P = 0.29); I^2 =19%

Test for overall effect: Z = 2.59 (P = 0.0097)



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Analysis 2.11. Comparison 2 Mortality and Morbidity, Outcome 11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Mortality and Morbidity

Outcome: 11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adult Japanese MEGA Study	134/3958	182/4051		32.5 %	0.75 [0.61, 0.94]
AFCAPS/TexCAPS 1998	116/3304	183/3301		33.1 %	0.63 [0.50, 0.80]
CARDS 2004	134/1428	189/1410		34.4 %	0.70 [0.57, 0.86]
Total (95% CI)	**8690**	**8762**		**100.0 %**	**0.70 [0.61, 0.79]**

Total events: 384 (Statin Therapy Group), 554 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 1.17$, df = 2 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 5.66 (P < 0.00001)

Analysis 3.1. Comparison 3 Lipids, Outcome 1 Total Cholesterol.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Lipids

Outcome: 1 Total Cholesterol

Study or subgroup	Statin Therapy Group N	Mean(SD)	Usual Care or Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Adult Japanese MEGA Study	3958	-0.3 (0.31)	4051	-0.05 (0.31)		9.4 %	-0.25 [-0.26, -0.24]
ASPEN 2006	959	-0.51 (0.8)	946	-0.04 (0.8)		9.3 %	-0.47 [-0.54, -0.40]
CAIUS 1996	151	-1.01 (1.04)	154	0.18 (0.87)		9.0 %	-1.19 [-1.41, -0.97]
CARDS 2004	1428	-1.24 (0.84)	1410	-0.07 (0.87)		9.4 %	-1.17 [-1.23, -1.11]
CELL A 1996	111	-0.89 (0.86)	117	-0.18 (0.72)		9.0 %	-0.71 [-0.92, -0.50]
CELL B 1996	117	-0.86 (2.01)	110	0.07 (0.64)		8.3 %	-0.93 [-1.31, -0.55]
Derosa 2003	24	-1.63 (0.51)	23	-0.83 (0.58)		8.6 %	-0.80 [-1.11, -0.49]

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Study or subgroup	Statin Therapy Group N	Mean(SD)	Usual Care or Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
KAPS 1995	214	-1.5 (0.66)	212	0 (0.66)		9.3 %	-1.50 [-1.63, -1.37]
PHYLLIS A 2004	126	-1.07 (0.56)	127	-0.02 (0.41)		9.3 %	-1.05 [-1.17, -0.93]
PHYLLIS B 2004	128	-1.13 (0.52)	127	-0.24 (0.47)		9.3 %	-0.89 [-1.01, -0.77]
PREVEND IT 2004	433	-1 (1)	431	-0.2 (1.05)		9.2 %	-0.80 [-0.94, -0.66]
Total (95% CI)	**7649**		**7708**			**100.0 %**	**-0.89 [-1.20, -0.57]**

Heterogeneity: Tau² = 0.28; Chi² = 1521.63, df = 10 (P<0.00001); I² =99%

Test for overall effect: Z = 5.47 (P < 0.00001)

-1 -0.5 0 0.5 1

Favours treatment Favours control

Analysis 3.2. Comparison 3 Lipids, Outcome 2 LDL Cholesterol.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Lipids

Outcome: 2 LDL Cholesterol

Study or subgroup	Statin Therapy Group N	Mean(SD)	Usual Care or Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
ACAPS 1994	231	-1.1 (0.72)	230	-0.2 (0.69)		7.8 %	-0.90 [-1.03, -0.77]
Adult Japanese MEGA Study	3958	-0.47 (0.47)	4051	-0.08 (0.48)		8.1 %	-0.39 [-0.41, -0.37]
ASPEN 2006	959	-0.79 (0.67)	946	-0.01 (0.67)		8.0 %	-0.78 [-0.84, -0.72]
CAIUS 1996	151	-1.03 (0.86)	154	0.09 (0.74)		7.5 %	-1.12 [-1.30, -0.94]
CARDS 2004	1428	-0.93 (0.71)	1410	0.1 (0.75)		8.0 %	-1.03 [-1.08, -0.98]
CELL A 1996	111	-0.94 (0.89)	117	-0.21 (0.72)		7.3 %	-0.73 [-0.94, -0.52]
CELL B 1996	117	-0.96 (0.8)	110	-0.04 (0.64)		7.4 %	-0.92 [-1.11, -0.73]
Derosa 2003	24	-1.61 (0.57)	23	-0.61 (0.53)		6.5 %	-1.00 [-1.31, -0.69]
KAPS 1995	214	-1.4 (0.63)	212	0.2 (0.66)		7.8 %	-1.60 [-1.72, -1.48]
PHYLLIS A 2004	126	-1.03 (0.57)	127	-0.05 (0.44)		7.8 %	-0.98 [-1.11, -0.85]
PHYLLIS B 2004	128	-1.16 (0.47)	127	-0.25 (0.43)		7.9 %	-0.91 [-1.02, -0.80]
PREVEND IT 2004	433	-1 (0.95)	431	-0.1 (0.95)		7.8 %	-0.90 [-1.03, -0.77]

-1 -0.5 0 0.5 1

Favours treatment Favours control

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Study or subgroup	Statin Therapy Group N	Mean(SD)	Usual Care or Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
WOSCOPS 1997	3302	-0.7 (0.71)	3293	0 (0.71)		8.1 %	-0.70 [-0.73, -0.67]
Total (95% CI)	**11182**		**11231**			**100.0 %**	**-0.92 [-1.10, -0.74]**

Heterogeneity: Tau^2 = 0.11; Chi^2 = 1118.47, df = 12 (P<0.00001); I^2 =99%

Test for overall effect: Z = 9.90 (P < 0.00001)

Analysis 4.1. Comparison 4 Treatment Compliance, Outcome 1 Treatment Compliance.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 4 Treatment Compliance

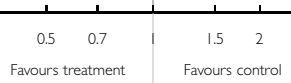
Outcome: 1 Treatment Compliance

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AFCAPS/TexCAPS 1998	2335/3304	2081/3301		27.6 %	1.12 [1.08, 1.16]
KAPS 1995	197/214	192/212		24.4 %	1.02 [0.96, 1.08]
PREVEND IT 2004	321/433	286/431		20.1 %	1.12 [1.02, 1.22]
WOSCOPS 1997	2311/3302	2305/3293		27.9 %	1.00 [0.97, 1.03]
Total (95% CI)	**7253**	**7237**		**100.0 %**	**1.06 [0.99, 1.14]**

Total events: 5164 (Statin Therapy Group), 4864 (Usual Care or Placebo)

Heterogeneity: Tau^2 = 0.00; Chi^2 = 26.73, df = 3 (P<0.00001); I^2 =89%

Test for overall effect: Z = 1.64 (P = 0.10)



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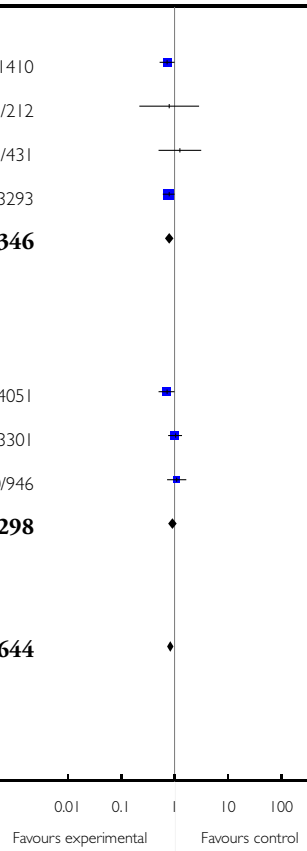
Analysis 5.1. Comparison 5 Sensitivity Analysis, Outcome 1 Randomisation for Total Mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 1 Randomisation for Total Mortality

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
CARDS 2004	61/1428	82/1410		19.3 %	0.73 [0.53, 1.01]
KAPS 1995	4/214	5/212		1.2 %	0.79 [0.22, 2.91]
PREVEND IT 2004	10/433	8/431		1.9 %	1.24 [0.50, 3.12]
WOSCOPS 1997	106/3302	135/3293		31.6 %	0.78 [0.61, 1.01]
Subtotal (95% CI)	**5377**	**5346**		**53.9 %**	**0.78 [0.65, 0.95]**
Total events: 181 (Statin Therapy Group), 230 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.12, df = 3 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 2.53 (P = 0.012)					
2 Randomisation method not known					
Adult Japanese MEGA Study	57/3958	81/4051		18.7 %	0.72 [0.51, 1.01]
AFCAPS/TexCAPS 1998	80/3304	77/3301		18.0 %	1.04 [0.76, 1.41]
ASPEN 2006	44/959	40/946		9.4 %	1.09 [0.71, 1.65]
Subtotal (95% CI)	**8221**	**8298**		**46.1 %**	**0.92 [0.75, 1.12]**
Total events: 181 (Statin Therapy Group), 198 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 3.22, df = 2 (P = 0.20); I^2 =38%					
Test for overall effect: Z = 0.83 (P = 0.40)					
Total (95% CI)	**13598**	**13644**		**100.0 %**	**0.84 [0.74, 0.97]**
Total events: 362 (Statin Therapy Group), 428 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 5.71, df = 6 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.016)					



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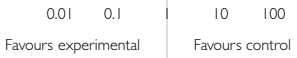
Analysis 5.2. Comparison 5 Sensitivity Analysis, Outcome 2 Randomisation for Fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 2 Randomisation for Fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
CAIUS 1996	1/151	0/154		0.5 %	3.06 [0.13, 74.51]
KAPS 1995	2/214	2/212		1.9 %	0.99 [0.14, 6.97]
PREVEND IT 2004	9/433	16/431		15.3 %	0.56 [0.25, 1.25]
WOSCOPS 1997	38/3302	52/3293		49.7 %	0.73 [0.48, 1.10]
Subtotal (95% CI)	**4100**	**4090**		**67.4 %**	**0.71 [0.50, 1.02]**
Total events: 50 (Statin Therapy Group), 70 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.27, df = 3 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 1.84 (P = 0.066)					
2 Randomisation method not known					
AFCAPS/TexCAPS 1998	11/3304	15/3301		14.3 %	0.73 [0.34, 1.59]
ASPEN 2006	24/959	19/946		18.3 %	1.25 [0.69, 2.26]
Subtotal (95% CI)	**4263**	**4247**		**32.6 %**	**1.02 [0.64, 1.63]**
Total events: 35 (Statin Therapy Group), 34 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.13, df = 1 (P = 0.29); I^2 =12%					
Test for overall effect: Z = 0.08 (P = 0.93)					
Total (95% CI)	**8363**	**8337**		**100.0 %**	**0.81 [0.61, 1.08]**
Total events: 85 (Statin Therapy Group), 104 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 3.84, df = 5 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.42 (P = 0.15)					



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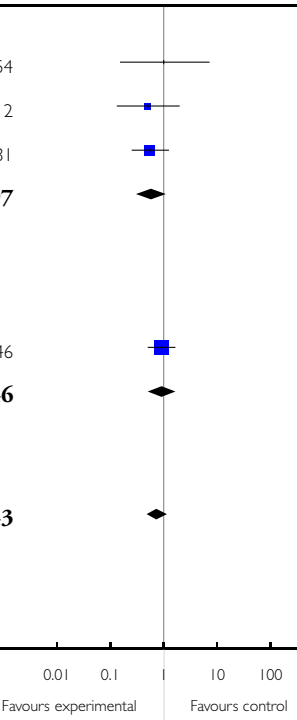
Analysis 5.3. Comparison 5 Sensitivity Analysis, Outcome 3 Randomisation for Non-fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 3 Randomisation for Non-fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
CAIUS 1996	2/151	2/154		4.3 %	1.02 [0.15, 7.15]
KAPS 1995	3/214	6/212		13.0 %	0.50 [0.13, 1.95]
PREVEND IT 2004	9/433	16/431		34.7 %	0.56 [0.25, 1.25]
Subtotal (95% CI)	**798**	**797**		**52.1 %**	**0.58 [0.30, 1.12]**
Total events: 14 (Statin Therapy Group), 24 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 1.63 (P = 0.10)					
2 Randomisation method not known					
ASPEN 2006	20/959	22/946		47.9 %	0.90 [0.49, 1.63]
Subtotal (95% CI)	**959**	**946**		**47.9 %**	**0.90 [0.49, 1.63]**
Total events: 20 (Statin Therapy Group), 22 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Total (95% CI)	**1757**	**1743**		**100.0 %**	**0.73 [0.47, 1.14]**
Total events: 34 (Statin Therapy Group), 46 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.29, df = 3 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					



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Analysis 5.4. Comparison 5 Sensitivity Analysis, Outcome 4 Randomisation for Fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

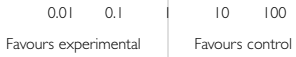
Outcome: 4 Randomisation for Fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
PREVEND IT 2004	4/433	4/431		5.2 %	1.00 [0.25, 3.95]
WOSCOPS 1997	50/3302	73/3293		94.8 %	0.68 [0.48, 0.98]
Total (95% CI)	**3735**	**3724**		**100.0 %**	**0.70 [0.50, 0.99]**

Total events: 54 (Statin Therapy Group), 77 (Usual Care or Placebo)

Heterogeneity: $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 2.03 (P = 0.042)



Analysis 5.5. Comparison 5 Sensitivity Analysis, Outcome 5 Randomisation for Non-fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

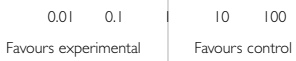
Outcome: 5 Randomisation for Non-fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
PREVEND IT 2004	18/433	21/431		100.0 %	0.85 [0.46, 1.58]
Total (95% CI)	**433**	**431**		**100.0 %**	**0.85 [0.46, 1.58]**

Total events: 18 (Statin Therapy Group), 21 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)



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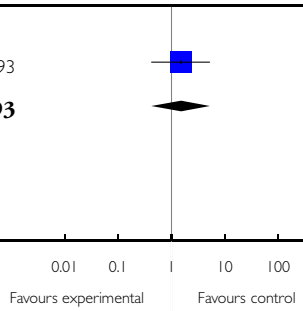
Analysis 5.6. Comparison 5 Sensitivity Analysis, Outcome 6 Randomisation for Fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 6 Randomisation for Fatal Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
WOSCOPS 1997	6/3302	4/3293		100.0 %	1.50 [0.42, 5.30]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**1.50 [0.42, 5.30]**
Total events: 6 (Statin Therapy Group), 4 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.53)					



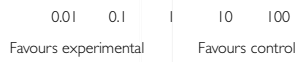
Analysis 5.7. Comparison 5 Sensitivity Analysis, Outcome 7 Randomisation for total number of fatal and non-fatal CHD, CVD and Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 7 Randomisation for total number of fatal and non-fatal CHD, CVD and Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Randomisation method known					
CARDS 2004	134/1428	189/1410		34.3 %	0.70 [0.57, 0.86]
Subtotal (95% CI)	**1428**	**1410**		**34.3 %**	**0.70 [0.57, 0.86]**
Total events: 134 (Statin Therapy Group), 189 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.35 (P = 0.00081)					
2 Randomisation method not known					
Adult Japanese MEGA Study	134/3958	182/3958		32.8 %	0.74 [0.59, 0.92]
AFCAPS/TexCAPS 1998	116/3304	183/3301		33.0 %	0.63 [0.50, 0.80]
Subtotal (95% CI)	**7262**	**7259**		**65.7 %**	**0.68 [0.58, 0.80]**
Total events: 250 (Statin Therapy Group), 365 (Usual Care or Placebo)					



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Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi^2 = 0.88, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 4.71 (P < 0.00001)					
Total (95% CI)	**8690**	**8669**	♦	**100.0 %**	**0.69 [0.61, 0.78]**
Total events: 384 (Statin Therapy Group), 554 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 0.90, df = 2 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 5.78 (P < 0.00001)					

0.01 0.1 1 10 100

Favours experimental Favours control

Analysis 5.8. Comparison 5 Sensitivity Analysis, Outcome 8 Study Size for Total Mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 8 Study Size for Total Mortality

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
Adult Japanese MEGA Study	57/3958	81/4051	■	18.7 %	0.72 [0.51, 1.01]
AFCAPS/TexCAPS 1998	80/3304	77/3301	■	18.0 %	1.04 [0.76, 1.41]
ASPEN 2006	44/959	40/946	■	9.4 %	1.09 [0.71, 1.65]
CARDS 2004	61/1428	82/1410	■	19.3 %	0.73 [0.53, 1.01]
WOSCOPS 1997	106/3302	135/3293	■	31.6 %	0.78 [0.61, 1.01]
Subtotal (95% CI)	**12951**	**13001**	♦	**97.0 %**	**0.84 [0.73, 0.96]**
Total events: 348 (Statin Therapy Group), 415 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 5.01, df = 4 (P = 0.29); I^2 =20%					
Test for overall effect: Z = 2.47 (P = 0.013)					
2 Under 1000 participants					
KAPS 1995	4/214	5/212	─	1.2 %	0.79 [0.22, 2.91]
PREVEND IT 2004	10/433	8/431	─	1.9 %	1.24 [0.50, 3.12]
Subtotal (95% CI)	**647**	**643**	◆	**3.0 %**	**1.07 [0.51, 2.26]**
Total events: 14 (Statin Therapy Group), 13 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					

0.01 0.1 1 10 100

Favours experimental Favours control

(*Continued* . . .)

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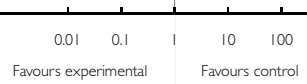
Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**13598**	**13644**		**100.0 %**	**0.84 [0.74, 0.97]**
Total events: 362 (Statin Therapy Group), 428 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 5.71, df = 6 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.016)					



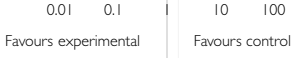
Analysis 5.9. Comparison 5 Sensitivity Analysis, Outcome 9 Study Size for Fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 9 Study Size for Fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
AFCAPS/TexCAPS 1998	11/3304	15/3301		14.3 %	0.73 [0.34, 1.59]
ASPEN 2006	24/959	19/946		18.3 %	1.25 [0.69, 2.26]
WOSCOPS 1997	38/3302	52/3293		49.7 %	0.73 [0.48, 1.10]
Subtotal (95% CI)	**7565**	**7540**		**82.3 %**	**0.84 [0.62, 1.15]**
Total events: 73 (Statin Therapy Group), 86 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 2.25, df = 2 (P = 0.32); I^2 =11%					
Test for overall effect: Z = 1.07 (P = 0.28)					
2 Under 1000 participants					
CAIUS 1996	1/151	0/154		0.5 %	3.06 [0.13, 74.51]
KAPS 1995	2/214	2/212		1.9 %	0.99 [0.14, 6.97]
PREVEND IT 2004	9/433	16/431		15.3 %	0.56 [0.25, 1.25]
Subtotal (95% CI)	**798**	**797**		**17.7 %**	**0.67 [0.33, 1.37]**
Total events: 12 (Statin Therapy Group), 18 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.22, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.09 (P = 0.27)					
Total (95% CI)	**8363**	**8337**		**100.0 %**	**0.81 [0.61, 1.08]**
Total events: 85 (Statin Therapy Group), 104 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 3.84, df = 5 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.42 (P = 0.15)					



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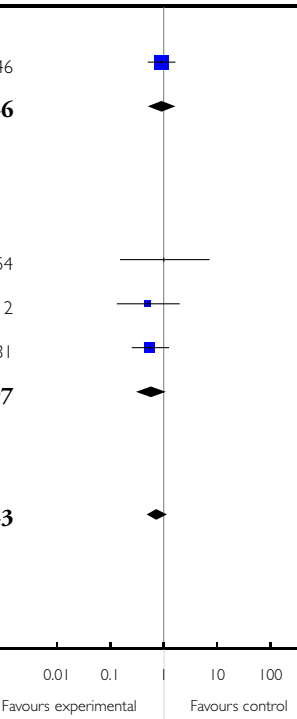
Analysis 5.10. Comparison 5 Sensitivity Analysis, Outcome 10 Study Size for Non-fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 10 Study Size for Non-fatal CHD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
ASPEN 2006	20/959	22/946		47.9 %	0.90 [0.49, 1.63]
Subtotal (95% CI)	**959**	**946**		**47.9 %**	**0.90 [0.49, 1.63]**
Total events: 20 (Statin Therapy Group), 22 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
2 Under 1000 participants					
CAIUS 1996	2/151	2/154		4.3 %	1.02 [0.15, 7.15]
KAPS 1995	3/214	6/212		13.0 %	0.50 [0.13, 1.95]
PREVEND IT 2004	9/433	16/431		34.7 %	0.56 [0.25, 1.25]
Subtotal (95% CI)	**798**	**797**		**52.1 %**	**0.58 [0.30, 1.12]**
Total events: 14 (Statin Therapy Group), 24 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 1.63 (P = 0.10)					
Total (95% CI)	**1757**	**1743**		**100.0 %**	**0.73 [0.47, 1.14]**
Total events: 34 (Statin Therapy Group), 46 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 1.29, df = 3 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					



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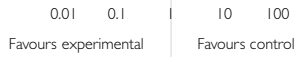
Analysis 5.11. Comparison 5 Sensitivity Analysis, Outcome 11 Study Size for Fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 11 Study Size for Fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
WOSCOPS 1997	50/3302	73/3293		94.8 %	0.68 [0.48, 0.98]
Subtotal (95% CI)	**3302**	**3293**		**94.8 %**	**0.68 [0.48, 0.98]**
Total events: 50 (Statin Therapy Group), 73 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.10 (P = 0.036)					
2 Under 1000 participants					
PREVEND IT 2004	4/433	4/431		5.2 %	1.00 [0.25, 3.95]
Subtotal (95% CI)	**433**	**431**		**5.2 %**	**1.00 [0.25, 3.95]**
Total events: 4 (Statin Therapy Group), 4 (Usual Care or Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
Total (95% CI)	**3735**	**3724**		**100.0 %**	**0.70 [0.50, 0.99]**
Total events: 54 (Statin Therapy Group), 77 (Usual Care or Placebo)					
Heterogeneity: Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 2.03 (P = 0.042)					



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Analysis 5.12. Comparison 5 Sensitivity Analysis, Outcome 12 Study Size for Non-fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

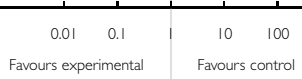
Outcome: 12 Study Size for Non-fatal CVD Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Under 1000 participants					
PREVEND IT 2004	18/433	21/431		100.0 %	0.85 [0.46, 1.58]
Total (95% CI)	**433**	**431**		**100.0 %**	**0.85 [0.46, 1.58]**

Total events: 18 (Statin Therapy Group), 21 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)



Analysis 5.13. Comparison 5 Sensitivity Analysis, Outcome 13 Study Size for Fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 13 Study Size for Fatal Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
WOSCOPS 1997	6/3302	4/3293		100.0 %	1.50 [0.42, 5.30]
Total (95% CI)	**3302**	**3293**		**100.0 %**	**1.50 [0.42, 5.30]**

Total events: 6 (Statin Therapy Group), 4 (Usual Care or Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)

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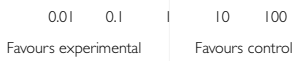
Analysis 5.14. Comparison 5 Sensitivity Analysis, Outcome 14 Study Size for total number of fatal and non-fatal CHD, CVD and stroke events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 14 Study Size for total number of fatal and non-fatal CHD, CVD and stroke events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Over 1000 participants					
Adult Japanese MEGA Study	134/3958	182/4051		32.5 %	0.75 [0.61, 0.94]
AFCAPS/TexCAPS 1998	116/3304	183/3301		33.1 %	0.63 [0.50, 0.80]
CARDS 2004	134/1428	189/1410		34.4 %	0.70 [0.57, 0.86]
Total (95% CI)	**8690**	**8762**		**100.0 %**	**0.70 [0.61, 0.79]**
Total events: 384 (Statin Therapy Group), 554 (Usual Care or Placebo)					
Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² =0.0%					
Test for overall effect: Z = 5.66 (P < 0.00001)					



APPENDICES

Appendix 1. Search Strategy

CENTRAL on The Cochrane Library

#1MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees
#2 statin or statins
#3 atorvastatin
#4 cerivastatin
#5 fluvastatin
#6 lovastatin
#7 pravastatin
#8 simvastatin
#9 lipitor
#10 baycol
#11 lescol
#12 mevacor
#13 altocor
#14 pravachol
#15 lipostat
#16 zocor
#17 rosuvastatin
#18 (hydroxymethylglutaryl next coenzyme next reductase next inhibitor)

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#19 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#20 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#21 (#19 or #20)

MEDLINE on Ovid

1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2 (statin or statins).tw.
3 atorvastatin.tw.
4 cerivastatin.tw.
5 fluvastatin.tw.
6 lovastatin.tw.
7 pravastatin.tw.
8 simvastatin.tw.
9 lipitor.tw.
10 baycol.tw.
11 lescol.tw.
12 mevacor.tw.
13 altocor.tw.
14 pravachol.tw.
15 lipostat.tw.
16 zocor.tw.
17 mevinolin.tw.
18 compactin.tw.
19 fluindostatin.tw.
20 rosuvastatin.tw.
21 or/1-20
22 exp Cardiovascular Diseases/
23 cardiovascular.tw.
24 heart disease$.tw.
25 coronary disease$.tw.
26 angina.tw.
27 heart failure.tw.
28 cardiac failure.tw.
29 exp Hyperlipidemia/
30 hyperlipid$.tw.
31 hypercholesterol$.tw.
32 exp Cholesterol/
33 cholesterol$.tw.
34 randomized controlled trial.pt.
35 controlled clinical trial.pt.
36 Randomized controlled trials/
37 random allocation.sh.
38 double blind method.sh.
39 single-blind method.sh.
40 or/34-39
41 exp animal/ not human/
42 40 not 41
43 clinical trial.pt.
44 exp Clinical trials/
45 (clin$ adj25 trial$).ti,ab.
46 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
47 placebos.sh.

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48 placebo$.ti,ab.
49 random$.ti,ab.
50 research design.sh.
51 or/43-50
52 51 not 41
53 42 or 52
54 or/22-33
55 21 and 54 and 53

EMBASE on Ovid

1 exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
2 (statin or statins).tw.
3 atorvastatin.tw.
4 cerivastatin.tw.
5 fluvastatin.tw.
6 lovastatin.tw.
7 pravastatin.tw.
8 simvastatin.tw.
9 lipitor.tw.
10 baycol.tw.
11 lescol.tw.
12 mevacor.tw.
13 altocor.tw.
14 pravachol.tw.
15 lipostat.tw.
16 zocor.tw.
17 mevinolin.tw.
18 compactin.tw.
19 fluindostatin.tw.
20 rosuvastatin.tw.
21 or/1-20
22 exp Cardiovascular Disease/
23 cardiovascular.tw.
24 heart disease$.tw.
25 coronary disease$.tw.
26 angina.tw.
27 heart failure.tw.
28 cardiac failure.tw.
29 exp Hyperlipidemia/
30 hyperlipid$.tw.
31 hypercholesterol$.tw.
32 exp Cholesterol/
33 cholesterol$.tw.
34 exp lipid blood level/
35 or/22-34
36 21 and 35
37 random$.ti,ab.
38 factorial$.ti,ab.
39 (crossover$ or cross over$ or cross-over$).ti,ab.
40 placebo$.ti,ab.
41 (double$ adj blind$).ti,ab.
42 (singl$ adj blind$).ti,ab.

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43 assign$.ti,ab.
44 allocat$.ti,ab.
45 volunteer$.ti,ab.
46 Crossover Procedure/
47 Double Blind Procedure/
48 Randomized Controlled Trial/
49 Single Blind Procedure/
50 or/37-49
51 exp animal/
52 nonhuman/
53 exp animal experiment/
54 or/51-53
55 exp human/
56 54 not 55
57 50 not 56
58 36 and 57

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2011

CONTRIBUTIONS OF AUTHORS

Professor Shah Ebrahim and Professor George Davey Smith: Origination of idea, preparation of review on which this review is based, control of content.

Fiona Taylor: Assessed relevance and quality of papers, extracted data, analysed data and prepared the manuscript.

Juan Pablo Casas: Contributed to preparing the manuscript

Kirsten Ward: Obtained papers, assessed relevance and quality of papers, extracted data, organised and analysed data.

Theresa Moore: Contributed to the early work on this review.

Margaret Burke: Developed search strategy, ran searches and assessed relevance of papers.

DECLARATIONS OF INTEREST

None known.

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