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Statins for the primary prevention of cardiovascular disease (Review)

Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, Ward K, Ebrahim S

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Statins for the primary prevention of cardiovascular disease (Review)

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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 CVD 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 CVD. The case for primary prevention was uncertain when the last version of this review was published (2011) and in light of new data an update of this review is required.

Objectives

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

Search methods

To avoid duplication of effort, we checked reference lists of previous systematic reviews. The searches conducted in 2007 were updated in January 2012. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2022, Issue 4), MEDLINE OVID (1950 to December Week 4 2011) and EMBASE OVID (1980 to 2012 Week 1). There were no language restrictions.

Selection criteria

We included randomised controlled trials of statins versus placebo or usual care control with minimum treatment duration of one year and follow-up of six months, in adults with no restrictions on total, low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol levels, and where 10% or less had a history of CVD.

Data collection and analysis

Two review 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), revascularisation, change in total and LDL cholesterol concentrations, adverse events, quality of life and costs. Odds ratios (OR) and risk ratios (RR)

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were calculated for dichotomous data, and for continuous data, pooled mean differences (MD) (with 95% confidence intervals (CI)) were calculated. We contacted trial authors to obtain missing data.

Main results

The latest search found four new trials and updated follow-up data on three trials included in the original review. Eighteen randomised control trials (19 trial arms; 56,934 participants) were included. Fourteen trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (OR 0.86, 95% CI 0.79 to 0.94); as was combined fatal and non-fatal CVD RR 0.75 (95% CI 0.70 to 0.81), combined fatal and non-fatal CHD events RR 0.73 (95% CI 0.67 to 0.80) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89). Reduction of revascularisation rates (RR 0.62, 95% CI 0.54 to 0.72) was also seen. Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no evidence of any serious harm caused by statin prescription. Evidence available to date showed that primary prevention with statins is likely to be cost-effective and may improve patient quality of life. Recent findings from the Cholesterol Treatment Trialists study using individual patient data meta-analysis indicate that these benefits are similar in people at lower (< 1% per year) risk of a major cardiovascular event.

Authors' conclusions

Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins.

PLAIN LANGUAGE SUMMARY

Statins for the primary prevention of cardiovascular disease

Cardiovascular disease (CVD), which comprises heart attacks (myocardial infarction), angina and strokes, is ranked as the number one cause of mortality and is a major cause of morbidity world wide. High blood cholesterol is linked to CVD events and is an important risk factor. Reducing high blood cholesterol, is thus an important way to reduce the chances of suffering a CVD event. Statins - cholesterol lowering drugs - (e.g. simvastatin, pravastatin, atorvastatin) are the first-choice treatments. Since the early statin randomised controlled trials were reported in the 1990s, several reviews of the effects of statins have been published highlighting their benefits particularly in people with a past history of CVD. Benefits include a reduction in CVD events. Statins have also been shown to reduce the risk of a first event in otherwise healthy individuals at high risk of CVD (primary prevention) but information on possible hazards has not been reported fully. The aim of this updated 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 2011. We found 18 randomised controlled trials with 19 trial arms (56,934 patients) dating from 1994 to 2008. All were randomised control trials comparing statins with usual care or placebo. The mean age of the participants was 57 years (range 28 - 97 years), 60.3% were men, and of the eight trials that reported on ethnicity, 85.9 % were Caucasian. Duration of treatment was a minimum one year and with follow-up of a minimum of six months. All-cause mortality and fatal and non-fatal CVD events were reduced with the use of statins as was the need for revascularisation (the restoration of an adequate blood supply to the heart) by means of surgery (coronary artery bypass graft) or by angioplasty (PTCA). Of 1000 people treated with a statin for five years, 18 would avoid a major CVD event which compares well with other treatments used for preventing cardiovascular disease. Taking statins did not increase the risk of serious adverse effects such as cancer. Statins are likely to be cost-effective in primary prevention.

BACKGROUND

Burden of cardiovascular disease

Cardiovascular disease (CVD) encompasses a wide range of disease including coronary heart disease (e.g. heart attack, angina), cerebrovascular disease (ischaemic and haemorrhagic stroke), raised blood pressure, hypertension, rheumatic heart disease and heart

failure. In the context of this review 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 as 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 requiring behavioural counselling. Those unable to achieve or maintain adequate risk reduction through lifestyle changes alone or those at high risk may benefit from pharmacotherapy. High blood cholesterol (hypercholesterolaemia) is a risk factor for both fatal and non-fatal CVD events in people with and without a past CVD (Prospective Studies Collaboration 2007), and lowering cholesterol, in particular low density lipoprotein (LDL) cholesterol, is an important target for pharmacotherapy. Statins are the first-choice agents for LDL cholesterol reduction. Since the relation between blood cholesterol and cardiovascular risk is continuous (Chen 1991), there is no definite threshold to initiate treatment. 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 disability-adjusted life years (DALYs) (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 higher dietary saturated fat intake and a lower ratio of polyunsaturated to saturated fatty acids have higher than average cholesterol levels (Davey Smith 1992).

Trial evidence for use of statins

Since the early statin trials were reported in the early 1990s, several reviews of the effects of statins have been published highlighting the benefits of their use (Baigent 2005; Bartlett 2003; Blauw 1997; Briel 2004; Cheung 2004; Ebrahim 1999; Katerndahl 1999; LaRosa 1994; LaRosa 1999; Law 2003; Pignone 2000; Silva 2006; Thavendiranathan 2006; Ward 2007; Wilt 2004). The Cholesterol Treatment Trialists (CTT) Collaboration has used individual patient data in their meta-analyses to show consistency of treatment benefits across a wide range of patient subgroups (Baigent 2005).

More recent evidence from the CCT Collaboration has demonstrated that statins are beneficial in reducing the risk of CVD events in people without prior evidence of CVD (CTT Collaboration 2010). A 2012 CTT Collaboration report further demonstrated a consistent 20% relative risk reduction in major vascular events with statins per 1 mmol/L reduction in LDL cholesterol, regardless of baseline risk (CTT Collaboration 2012a). Men and women, old and young, and people with and without CVD all appear to benefit. These findings confirm the efficacy of statins for primary prevention, resolving concerns about possible serious adverse effects and potential sources of bias in the randomised trials highlighted in an earlier version of this Cochrane review.

Adverse effects of statins

There has been some concern, primarily from observational studies, that low levels of blood cholesterol increase the risk of mortality from causes other than coronary heart disease (CHD), 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 were poorly reported and unclear in earlier trials (Jackson 2001), but among those with and without pre-existing CVD the evidence now 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). Individual patient data meta-analyses conducted by the CTT Collaboration have demonstrated unequivocally that there is no excess risk of cancers (CTT Collaboration 2012b), confirming the findings of an earlier review and has reported reductions in all-cause mortality and no excess of non-vascular mortality (Dale 2006). Rhabdomyolysis - break down of muscles - which can be serious if not detected and treated early (Beers 2003) may be caused by statins, but this is very rare. In a systematic review of randomised trials 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).

An increased risk of incident type 2 diabetes associated with statin therapy compared with usual care or placebo has been reported (Mills 2011; Sattar 2010) and with high dose versus usual dose statins (Preiss 2011). The mechanism by which statins may increase diabetes risk is not known. Haemorrhagic stroke appears to be increased by statin treatment, although estimates are imprecise, with an annual risk of 0.5 per 1000 patients treated for five years

which is small compared with the benefits seen on the overall risk of stroke (CTT Collaboration 2012a). Two recent meta-analyses of large-scale placebo or standard care controlled trials observed a 9% increased risk for incident diabetes associated with statin therapy, with little heterogeneity between studies. In Mills 2011 (Mills 2011), 17 randomised controlled trials (RCTs) reported an increased risk of the development of diabetes.

Other possible adverse events derived from small trials have been investigated. In a recent RCT of 1016 adults, statin treatment for six months was associated with increased self-reporting of reduced energy and fatigue on exertion (Golomb 2012). An earlier 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 the risk of death from non-illness mortality (accidents, violence or suicide) (Muldoon 2001).

Guidelines for use of statins

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. (Genest 2009; Manuel 2006; NICE 2006; Reiner 2011) Statin prescribing and expenditure have risen rapidly as a result. For example, the European statin prescription 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).

Why it is important to do this review

A major limitation of the evidence summaries to date is combining trials of statins in secondary and primary prevention of CVD without reporting benefits and adverse effects separately. A number of systematic reviews have focused on statins in primary prevention, but they differ in their interpretation of the evidence (Brugts 2009; Ebrahim 1999; NICE 2006; Thavendiranathan 2006; Vreecer, 2003; Ward 2007). This is largely due to the differing inclusion criteria of the reviews and differences in reporting of outcomes. The most recent systematic review, using individual participant data from the majority of statin trials, provides strong evidence that benefits from statins outweigh any possible serious adverse effects, even at very low levels of CVD event rates (CTT Collaboration 2012a). These new findings counter earlier opinion that the evidence is insufficient to support use of statins in primary prevention

for women or in older men (Abramson 2007). Previous reviews, in addition, have not reported other relevant outcomes such as costs, patient quality of life nor have they focused their attention on detailed reporting of adverse side effects.

The aim of this systematic review is to update and include further trials that have been published since the last search (to 2007) and contextualise our findings with those recently published by the CTT Collaboration.

OBJECTIVES

To update this review 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 than or equal to 10% of a previous history of CVD (this would include previous angina, myocardial infarction and/or stroke). Trials in which statins were used to treat or control chronic conditions (e.g. Alzheimer's disease, rheumatoid arthritis, renal disease, macular degeneration, aortic stenosis) were excluded.

Types of interventions

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

Concomitant interventions

Drug treatments and other interventions were accepted provided they were 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 and low density lipoprotein (LDL) 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. The searches conducted in 2007 (Appendix 1) were updated on 10th January 2012 (Appendix 2). We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (2011, Issue 4), MEDLINE OVID (1950 to December Week 4 2011) and EMBASE OVID (1980 to 2012 Week 1). The standard RCT filters used for MEDLINE and EMBASE (Lefebvre 1996) in 2007 were updated in 2012. The Cochrane sensitivity- and precision-maximising RCT filter has been applied to the MEDLINE search (Lefebvre 2011) and the BMJ 2011 has been applied to the EMBASE search. No language restrictions were applied to either searching or trial inclusion. 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 review authors 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 (FT and KW for the original review, FT and AM for the update). Full articles were retrieved for further assessment. The articles were read independently by two review authors (FT and KW for the original review, FT and AM for the update) 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 for Systematic Reviews of Interventions* 5.0.2 (Higgins 2011).

Assessment of risk of bias

We used criteria described in the *Cochrane Handbook of Systematic Reviews* 5.0.2 (Higgins 2011) to describe the quality of trials

we found. Two review authors independently assessed risk of bias of selected studies (FT and KW for the original review, FT and AM for the update). 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 for Systematic Reviews of Interventions*.

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 was centralised or pharmacy-controlled, or where the following were 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 highlighted any selective outcome reporting.

A 'Risk of bias' graph for each trial was made available to assess quality.

Data extraction

We designed a data extraction form and included data on our outcomes measures in addition to:

- study ID;
- quality;
- population characteristics terms of CVD risk;
- 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 and LDL cholesterol.

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

Contacting trialists

For unpublished studies or where data were incomplete in published papers, we contacted trial authors to obtain further details.

Data analysis

Risk ratios (RR), odds ratio (OR) 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), we calculated pooled mean differences (MD) (with 95% CI).

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: 10 trials reported this as a composite outcome, but three reported on fatal and five 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 were considered to be heterogeneous where the I^2 statistic was $> 50\%$. For analysis, we used the fixed-effect method unless data were 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 asymmetry, which represents the presence of publication bias based on the data for the primary outcome of all-cause mortality (Sterne 2001).

Analyses for potential effect modifiers was initially considered but abandoned due to lack of adequate reporting. We planned to include:

- gender;
- extent of hyperlipidaemia;
- age greater than and less than 65 years.

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 large studies to see how they influence the results;
- post-hoc analysis (requested by a peer-reviewer) excluding those trials with any participants with clinical evidence of CVD.

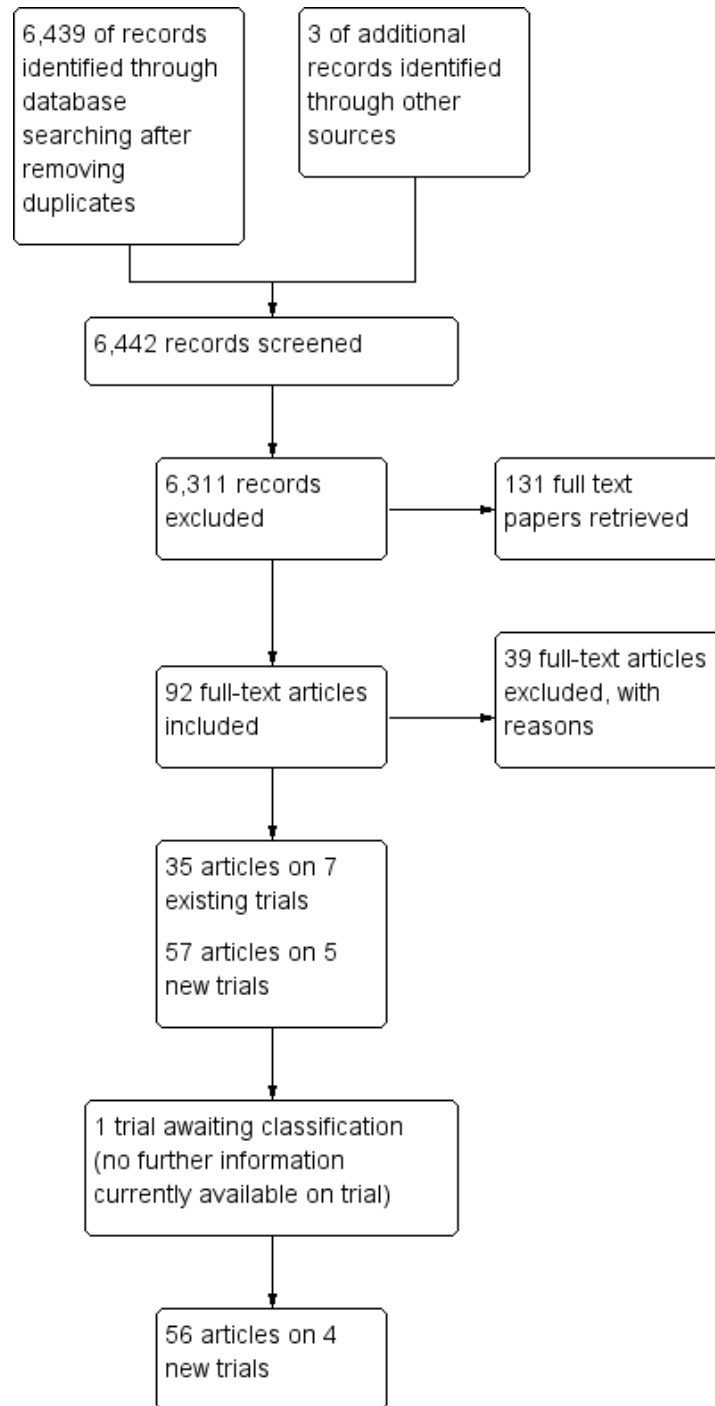
RESULTS

Description of studies

For the original review 4227 references were identified after removal of duplicates. 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](#)).

For this update, 6442 references were identified after removal of duplicates and of these, 131 full papers were retrieved. From these, 92 papers were relevant; 35 papers related to seven studies included in the original review and 57 papers to five new trials. For one of these (a conference abstract), we were unable to obtain further data (Babes 2010). This study is listed in the Table: [Characteristics of studies awaiting classification](#). We excluded 39 papers: 37 related to 36 excluded studies and two related to the previously excluded ASCOT-LLA trial (Figure 1). Reasons for exclusion remained unchanged and mainly included; treatment length not at least being one year, more than 10% of the population having existing CVD and no relevant outcomes (to this review) being reported (see [Characteristics of excluded studies](#)).

Figure 1. Study flow diagram for the update



Our update identified four new trials with 19,662 additional participants (Bone 2007; CERDIA 2004; METEOR 2010; JUPITER 2008) bringing a total of 18 trials. Of the 18, trials, one tested two different interventions and for the purpose for meta analysis, this trial was counted as two trials (in total 19 trial arms) (CELL A 1996; CELL B 1996). In addition, our updated search identified reporting of new follow-up data of the three of the 14 trials in the original review. (Adult Japanese MEGA Study; CARDS 2008; WOSCOPS).

The trials dated from 1994 to 2008 and were conducted worldwide, mainly in industrially developed countries (Japan, USA, Europe and JUPITER which included sites in South America, Israel, South Africa and Russia). Fourteen trials recruited patients with specific conditions: nine recruited participants with raised lipids, four with diabetes, two with hypertension and one with microalbuminuria.

All tested the effectiveness of statins compared with placebo; nine tested pravastatin 10 mg to 40 mg per day; two atorvastatin 10 mg to 80 mg per day; two fluvastatin 40 mg to 80 mg per day; two lovastatin 20 mg to 40 mg per day; two rosuvastatin 20 mg to 40 mg per day; and the remaining two simvastatin 20 mg to 40 mg per day (one of these had started patients on cerivastatin 0.4 mg per day which was replaced with simvastatin in August 2001). Five trials also included advice, counselling or information on health-behaviour modification such as diet, smoking cessation, or exercise.

In total, the 18 trials (with 19 trial arms) recruited 56,934 participants and observed outcomes ranging from one to 5.3 years. The size of the population recruited ranged from 47 to 17,802. The mean age of the participants was 57 years (range 28-97 years), 60.3% included male participants, and of the eight trials that reported on ethnicity, 85.9 % were Caucasian.

Three trials (AFCAPS/TexCAPS 1998; CARDS 2008; JUPITER 2008) were stopped prematurely because significant reductions in primary composite outcomes between the intervention and placebo had been observed. Overall, these trials had recruited 47% of the total study population and were stopped 1.4 to 3.0 years before the pre-specified end date.

Data on all-cause mortality were provided in 11 trials. Excluding the four trials whose primary outcome was change in size of carotid

artery and one whose primary endpoint was change in bone density, nine of the remaining trials chose a composite primary outcome. Ten trials provided data on fatal and 11 on non-fatal CHD events, and five trials provided data on fatal and two on non-fatal CVD events. Ten trials reported on combined stroke events, five provided data on non-fatal and three on fatal stroke events. Fourteen trials provided data on cholesterol and 12 on adverse events. Four trials provided economic costings, (CARDS 2008; JUPITER 2008; MRC/BHF Heart Protection; WOSCOPS) and one (CELL A 1996; CELL B 1996) provided data on patient perceived quality of life.

Excluding the four trials that solely recruited participants with diabetes, 1% to 20% of the participants had diabetes. Excluding the two trials that recruited participants with hypertension, the remaining studies recruited 15% to 67% with hypertension. The proportion of participants smoking ranged from 10% to 45% in the 17 trials that provided these data. We were unable to ascertain baseline lipid levels for three trials. Baseline total cholesterol levels ranged from 4.81 to 6.97 mmol/L (median 6.17 mmol/L), and LDL cholesterol from 2.8 to 4.95 mmol/L (median 4.1 mmol/L).

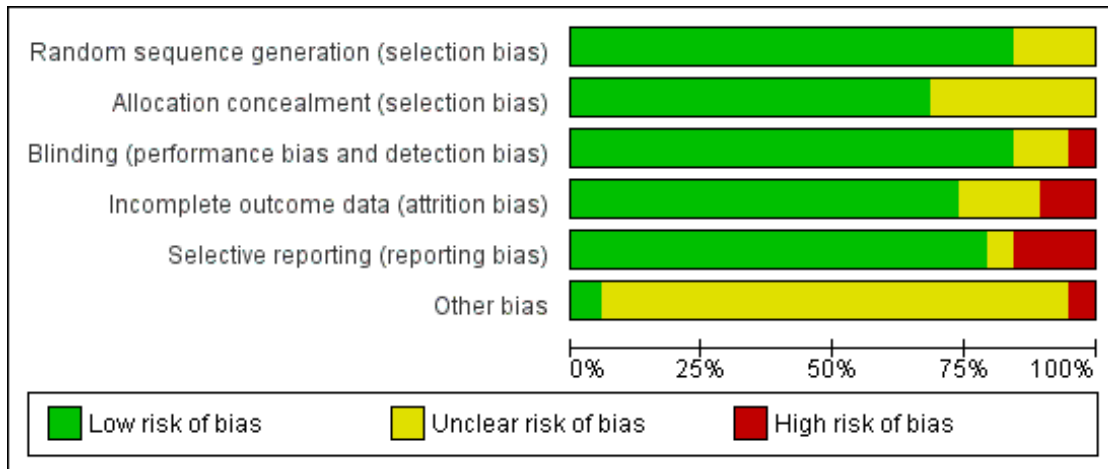
Risk of bias in included studies

In general, there was low risk of bias (Figure 2; Figure 3) though all trials were either fully or partially funded by pharmaceutical companies (five by Bristol Myers and Squibb, three by Pfizer, four by Astra-Zeneca, two by Merck and one by Bayer, one by Bayer and Merck, one by Pfizer, and the remaining by Sankyo Co Ltd). Three (AFCAPS/TexCAPS 1998; ASPEN 2006; HYRIM 2007) of the 19 trial arms did not provide adequate information on the methods used for randomisation, two of which had recruited more than 2,000 participants. Eighteen trials used blinding to reduce bias, 15 of which used double-blinding methods. Thirteen used intention-to-treat analysis. The drop-out rates ranged from 2% to 30% for the 12 trials that reported on this. We judged 15 of the trials to be free from selection bias. The MRC/BHF Heart Protection Study (MRC/BHF Heart Protection) only provided data on total CVD events for patients with diabetes in the primary prevention group, and HYRIM reported outcomes on cholesterol on a subset of the population (46%) with no explanation as to how the subset had been derived (HYRIM 2007).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

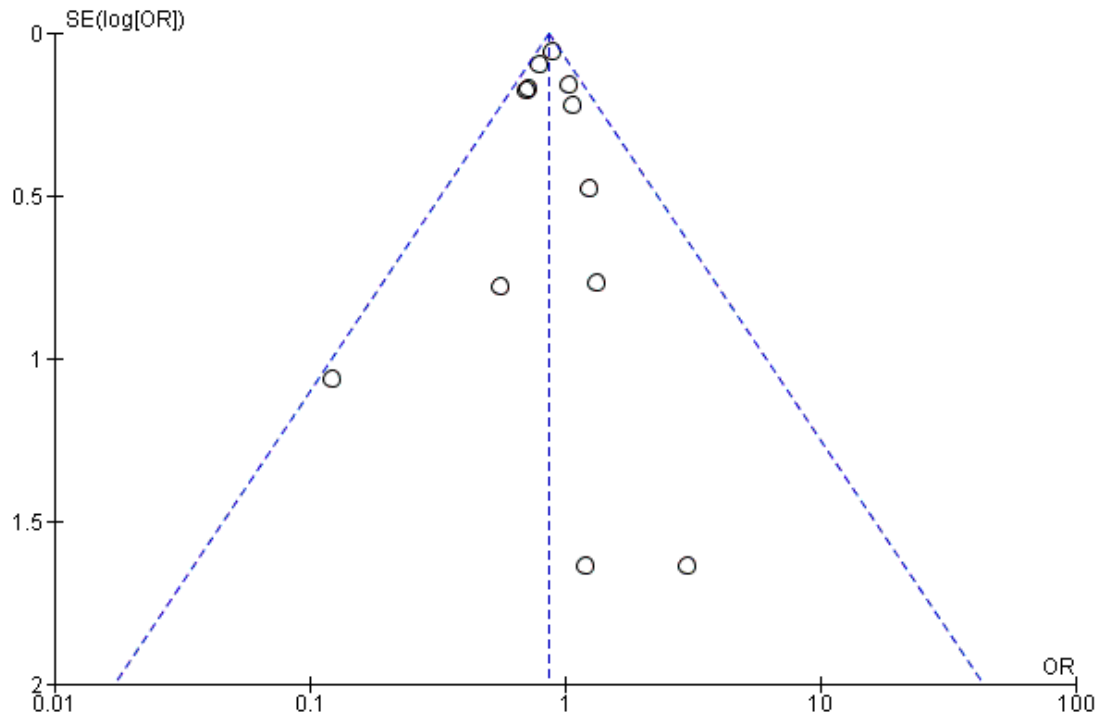
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ACAPS 1994	+	?	+	+	+	?
Adult Japanese MEGA Study	+	+	-	+	-	+
AFCAPS/TexCAPS 1998	?	?	+	+	+	?
ASPEN 2006	?	?	+	+	+	?
Bone 2007	+	+	?	+	+	?
CAIUS 1996	+	+	?	+	+	?
CARDS 2008	+	+	+	+	+	?
CELL A 1996	+	+	+	+	-	?
CELL B 1996	+	+	+	+	?	?
CERDIA 2004	+	?	+	-	+	?
Derosa 2003	+	+	+	+	+	?
HYRIM 2007	?	?	+	?	+	?
JUPITER 2008	+	+	+	+	+	-
KAPS 1995	+	+	+	-	+	?
METEOR 2010	+	+	+	+	+	?
MRC/BHF Heart Protection	+	+	+	?	-	?
PHYLLIS 2004	+	?	+	+	+	?
PREVEND IT 2004	+	+	+	?	+	?
WOSCOPS	+	+	+	+	+	?

Figure 3. 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 asymmetry (Figure 4).

Figure 4. Funnel plot of comparison: 2 Mortality and Morbidity, outcome: 2.1 Total Mortality.



Effects of interventions

All-cause mortality

Thirteen trials with 48,060 participants recruited reported on total mortality. During observation, 1077/24,408 (4.4%) died in the statin group compared with 1223/23,652 (5.1%) in the placebo group; yielding an unadjusted NNT for 5 years of 132 (95% confidence interval (CI) 121 to 144). Adjustment to account for total person-years of follow-up across all studies by dividing the number of events by total person-years of follow-up in the statin and placebo group from the included trials, yields an NNT for 5 years of 96 (95% CI 64 to 244). Only the JUPITER trial showed strong evidence of a reduction in total mortality. When the data were pooled using a fixed-effect model, a reduction that favoured statin treatment by 14% was observed: (odds ratio (OR) 0.86, 95% CI 0.79 to 0.94). No heterogeneity was observed (Analysis 1.1).

Fatal and non-fatal CHD events

Fourteen trials with 48,049 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-effect model: 820/24,217 (3.4%) in the statin group versus 1114/23,832 (4.6%) in the placebo group; yielding an unadjusted NNT for 5 years of 78 (95% confidence interval (CI) 72 to 85). Adjustment to account for total person-years of follow-up across all studies in the same manner as outlined above, yields an NNT for 5 years of 56 (95% CI 46 to 75); risk ratio (RR) 0.73 (95% CI 0.67 to 0.80) (Analysis 1.2).

Observations on fatal or non-fatal CHD events are based on 10 and 11 trials respectively. When pooled, a risk reduction in fatal CHD events was observed; 251/23,019 (1.1%) statin group versus 306/23,075 (1.3%) placebo group; RR 0.82 (95% CI 0.70 to 0.96) (Analysis 1.3). Evidence for a reduction in non-fatal CHD events was also found: 398/20,668 (1.9%) statin group versus 583/20,309 (2.8%); RR 0.67 (95% CI 0.59 to 0.76). No significant heterogeneity was observed using a fixed-effect model for both analyses (Analysis 1.4).

Fatal and non-fatal CVD events

Nine trials with 23,805 participants, representing 41.8% of the total population, reported on combined fatal and non-fatal CVD events. Four of the larger trials with 21,205 participants demonstrated strong evidence of a reduction in this combined outcome.

In the pooled analysis using a fixed-effect model: 1103/11,892 (9.3%) in the statin group versus 1455/11,913 (12.2%) in the placebo group; RR 0.75 (95% CI 0.70 to 0.81). There was no evidence of heterogeneity (Analysis 1.5).

Five trials reported on fatal CVD events and two reported on non-fatal CVD events. Reductions in risk were observed in both these endpoints; fatal CVD events; 295/16,962 (1.7%) in the statin group versus 355/17,050 (2.1%) in the placebo group; RR 0.83 (95% CI 0.72 to 0.96) (Analysis 1.6); non-fatal CVD events 123/4,299 (3%) in the statin group versus 175/4,398 (4%) in the placebo group, RR 0.77 (95% CI 0.62 to 0.96) (Analysis 1.7). No significant heterogeneity was observed using a fixed-effect model for both analyses.

Fatal and non-fatal stroke events

Ten trials with 40,295 participants reported on combined fatal and non-fatal stroke events. Two trials that had been stopped prematurely demonstrated a significant reduction in this combined outcome with the use of statins. This reduction was observed in the pooled analysis using a fixed-effect model: 345/20,302 (1.7%) in the statin group versus 442/19,993 (2.2%) in the placebo group; RR 0.78 (95% CI 0.68 to 0.89) (Analysis 1.8).

Three trials with 27,238 participants reported on fatal stroke events, and five trials with 28,097 participants reported on non-fatal stroke events. There was no observed difference in fatal stroke. We applied a random-effects model due to significant heterogeneity ($I^2 = 68%$). Two of three trials had been prematurely stopped, and the remaining trial (WOSCOPS) demonstrated a 43% increase in risk of fatal stroke, but this was not significant (Analysis 1.9). Using a fixed-effect model, a significant risk reduction was seen for non-fatal stroke events 193/14,243 (1.3%) in the statin group versus 276/13,852 (2%) in the placebo group; RR 0.69 (95% CI 0.58 to 0.83) Analysis 1.10.

Combined fatal and non-fatal CHD, CVD and stroke events

Only four trials with 35,254 participants reported a composite of fatal and non-fatal events for CHD, CVD and stroke. All the trials showed a significant reduction in this composite outcome with the treatment of statins, which was maintained in the pooled analysis and used a fixed model: 438/17,591 (2.4%) events versus 678/17,663 (3.8%); RR 0.65 (95% CI 0.58 to 0.73) (Analysis 1.11).

Revascularisation

Seven trials with 42,403 participants reported on the need for revascularisation procedures during follow-up: 286/21,166 (1.4%) in the statin group versus 461/21,237 (2.2%) in the placebo group underwent either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). Three

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. This was maintained in the pooled analysis using a fixed-effect model: RR 0.62 (0.54 to 0.72) (Analysis 1.12).

Cholesterol

Fourteen trials provided data on total cholesterol, and 16 trials provided data on LDL cholesterol. For both endpoints, all trials were able to demonstrate significant reductions. For total cholesterol, a net difference of -1.05 mmol/L (95% CI -1.35 to -0.76 mmol/L) was observed (Analysis 2.1), and for LDL cholesterol a net difference of -1.00 (95% CI -1.16 to -0.85 mmol/L) was observed (Analysis 2.2). There was marked heterogeneity of effects in both analysis ($I^2 = 100%$ and 99%, respectively). It is likely that the heterogeneity is due to differences in the type of statin and dosage used.

Adverse events

Twelve trials provided data on adverse events. In total 10,838/56,934 (19%) participants experienced an adverse event with adverse event rates ranging from 0% to 97%. Pooling the events rates indicated no difference between the intervention and control groups with the use of statin using a fixed-effect model: RR 1.00 (95% CI 0.97 to 1.03) (Analysis 3.1). No differences were observed between statin and control with the number of participants stopping statin treatment due to adverse events and those admitted to hospital for an adverse event, though heterogeneity was observed (Analysis 3.2; Analysis 3.3).

Cancer: 2255/38,739 (5.8%) participants in 11 trials developed cancer (Analysis 3.4). There was no evidence of any excess risk of cancers with a pooled estimate of RR 1.01 (95% CI 0.93 to 1.10) and no heterogeneity.

Myalgia and rhabdomyolysis: 3551/37,939 participants in nine trials developed myalgia, but there was no evidence of excess risk with a pooled estimate of 1.03 (95% CI 0.97 to 1.09) with some heterogeneity ($I^2 = 41%$) (Analysis 3.5). Rhabdomyolysis was very rare, affecting three of 19,410 participants on statins in six trials reporting this outcome but with no evidence of any excess risk on statins: RR 1.00 (95% CI 0.23 to 4.38) (Analysis 3.6). The Heart Protection Study outcomes for rhabdomyolysis were five cases in those on statins and three cases among controls, but these findings were not broken down by primary and secondary prevention. Adding these additional events to the estimate above gives RR 1.31 (95% CI 0.47 to 3.62).

Type 2 diabetes: reporting of new occurrences of type 2 diabetes was confined to only two trials, AFCAPS/TexCAPS 1998 and JUPITER 2008. Overall, 342/12,205 (2.8%) participants on statins developed diabetes compared with 290/12,202 (2.4%) participants on control or placebo, with a relative risk of developing

diabetes of 1.18 (95% CI 1.01 to 1.39). This excess risk of diabetes was driven by the JUPITER trial, which used higher statin doses than the AFACPS/TexCAPS trial, which showed no effect on diabetes incidence (Analysis 3.7).

Haemorrhagic stroke: only two trials reported haemorrhagic stroke outcomes which occurred in 45/25634 (0.2%) participants with a RR of 0.97 (95% CI 0.54 to 1.75) (Analysis 3.8).

Other adverse events: weak evidence was found for an increased risk of liver enzyme elevations (10 studies) RR 1.16 (95% CI 0.87 to 1.54) (Analysis 3.9), renal dysfunction (four studies) RR 1.11 (95% CI 0.99 to 1.26) (Analysis 3.10), and arthritis (two studies) RR 1.20 (95% CI 0.82 to 1.75) (Analysis 3.11).

Treatment compliance

Of the eight trials that reported treatment compliance there was no difference between the two groups (Analysis 4.1). In the statin group 77% participants and 70% in the placebo group complied with treatment; RR 1.08 (0.98 to 1.18).

Costs

Four trials reported on costs. WOSCOPS found that the use of statin yielded substantial health benefits at a cost which was not prohibitive: an undiscounted gain of 2460 years of life at a cost of £8,121 per life year gained (WOSCOPS). In the JUPITER trial, the authors estimated that rosuvastatin therapy was cost-effective, using a willingness-to-pay threshold of £31,882/QALY, statin therapy had a cost-effectiveness of £25,796/QALY for CHD and stroke prevention. (JUPITER 2008-Ohsfeldt 2010) The authors of CARDS estimated the cost of managing CVD events would be lower after five years for patients treated with atorvastatin compared with those on placebo. The cost-effectiveness of atorvastatin 10 mg/day would be £87,525/QALY at five years, with an incremental cost of £2,320/QALY at 10 years. (CARDS 2008-Ramsay 2008)

Patient quality of life

There were no reliable data on patient quality of life reported by trials. CELL A+B provided limited data on quality of life, suggesting that the intervention of lifestyle advice plus pravastatin reduced stress and sleeping problems.

Sensitivity analysis

We were unable to locate any unpublished studies. As the study quality was overall rated as good, for the update we confined our sensitivity analysis to comparing studies that were stopped early and followed a protocol and to comparing large and small studies for total mortality and total CHD events. These analyses indicated no change in the overall results in early stopping of trials and for

study size for either outcome (Analysis 5.1; Analysis 5.2 Analysis 5.3; Analysis 5.4).

Excluding the five trials that included up to 10% participants with clinical evidence of CVD (none of the trials published the subgroup without any evidence of CVD) demonstrates very similar findings: total mortality RR 0.80 (95% CI 0.70 to 0.91) versus RR 0.86 (0.79 to 0.94) in all trials; total CHD events RR 0.68 (0.59 to 0.77) versus 0.73 (0.67 to 0.80) in all trials; adverse events RR 0.99 (0.96 to 1.02) versus 1.00 (0.97 to 1.03) in all trials.

DISCUSSION

The trials included in this systematic review showed reductions in all-cause mortality, composite cardiovascular disease (CVD) endpoints, fatal and non-fatal CVD events considered separately, total and low density lipoprotein (LDL) cholesterol, and revascularisations. These findings were associated with falls in total and LDL cholesterol in all trials reporting these outcomes. No excess of combined adverse events, cancers, myopathy, rhabdomyolysis, haemorrhagic stroke, liver enzyme elevation, renal dysfunction and arthritis were found, although not all trials reported fully on adverse events. An increased risk of incident diabetes was found in the two trials reporting this outcome. There was limited evidence to suggest that the use of statins for primary prevention may be cost-effective. However, in light of new evidence derived from the CTT Collaboration on primary prevention, there is a need to update existing cost-effective analysis. Patient perceived quality of life was reported in only one trial, which showed limited benefit. Sensitivity analysis suggested that early stopping of trials and size of trial did not influence the overall results.

Although the trials intended to recruit only people without evidence of CVD, some trials did include some 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. A sensitivity analysis, excluding the five trials that had up to 10% participants with clinical evidence of CVD at baseline, showed very little difference between effect sizes compared with all the trials included in this review. Our findings concur with previous systematic reviews (Brugts 2009; Ebrahim 1999; NICE 2006). However, previous systematic reviews have included trials where more than 10% of participants had a previous history of CVD which is reflected in their higher baseline all-cause mortality event rates which were 1.4 per 100 person years at risk (NICE 2006) and 1.7 per 100 person years (Brugts 2009) compared with 1.0 per 100 person years in this review.

The CTT Collaboration has published analyses focusing on the comparison between high and low doses of statins which demonstrate that more intensive treatment lowers LDL cholesterol more, resulting in greater benefits (CTT Collaboration 2010) with no excess risk of non-vascular mortality. However, a increase in the

risk of myopathy and rhabdomyolysis in people treated with statins is confirmed, particularly among those treated with higher rather than lower doses statins (Armitage 2007). Strong evidence of the absence of any adverse effects on cancer risk is also confirmed by a further CTT Collaboration report (CTT Collaboration 2012b).

Our estimates of effects on CVD outcomes and on all-cause mortality on statins are in line with the recent CTT Collaboration report (CTT Collaboration 2012a). The major finding of this new report is the benefits from statins at low levels of CVD risk: six and 15 major vascular events would be avoided per 1000 people treated for five years in the two lowest baseline risk categories (< 5% five-year risk, RR 0.57 (0.36 to 0.89) and 5% to 10% five-year risk RR 0.61 (0.50 to 0.74)) respectively (Figure 1, CTT report), giving NNT values of 167 and 67 respectively. These NNTs are well within the range considered worthwhile in primary prevention (e.g. for treatment of hypertension).

The individual patient data analyses conducted by the CTT Collaboration counter concerns about the interpretation of the evidence of statins for primary prevention. First, the use of composite endpoints derived from different CVD outcomes is overcome since there is sufficient power to demonstrate benefits for individual CVD outcomes. Second, additional data on outcomes are available for most trials, which reduces any effect of selective reporting of outcomes. Third, similar benefits of statins were seen in trials that stopped early and in those running their planned course. Fourth, concerns about effects in low-risk groups, particularly women, are now demonstrated to be similar to those in other trial participants. Fifth, the benefits of statins outweigh any risks of serious adverse effects since no excess of cancers was found and all-cause mortality was lower in those on statins. Thus, earlier claims that statins provide no overall benefit in primary prevention in terms of all-cause mortality (Therapeutics Letter 2003; Therapeutics Letter 2010; Ray 2010) can no longer be substantiated.

Haemorrhagic stroke may be increased by use of statins with an annual excess risk of 0.5 per 1000 people treated over five years per 1.0 mmol/L LDL cholesterol reduction reported by the CTT Collaboration. However, overall stroke events were reduced, indicating a net benefit. This might not be the case in Asian populations where haemorrhagic stroke is more common than ischaemic stroke, and where evidence of association between low blood cholesterol and haemorrhagic stroke has been reported (Ebrahim 2006).

Our review, with sparse data, found an increased risk of type 2 diabetes in those treated with statins: RR 1.18 (95% CI 1.01 to 1.39), which is greater than the that found in a more comprehensive meta-analysis using both published and unpublished data from 13 trials (both primary and secondary prevention) which reported a relative risk of 1.09; 95% CI 1.02 to 1.17, with a number needed to harm of 255 people treated for four years to result in one case of diabetes (Preiss 2011; Sattar 2010). This increased

risk of diabetes appears to be related to baseline fasting glucose levels and metabolic syndrome among participants randomised to statins (Waters 2011). It can be argued that the overall small proportion of people who develop diabetes when treated with a statin is outweighed by the benefits of statins (CTT Collaboration 2012a). However, in the context of primary prevention, patients may expect not to be harmed in any way by 'preventive' treatments. Patient view points of such trade-offs remain to be assessed and will be important in determining wider use of statins (Smeeth 2012).

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). The reporting of adverse events in these trials is generally poor, with failure to provide details of severity and type of adverse events or to report on health-related quality of life. However, it seems unlikely that any major life-threatening hazards associated with statin use exist. Potential non-fatal but serious hazards of long-term statin use have not been assessed in trials (e.g. possible cognitive impairments suggested by one small trial: Muldoon 2000). We have focused on adverse events arising in randomised trial populations but these cannot adequately assess rare hazards, such as rhabdomyolysis. Large observational databases are useful for detecting rare hazards associated with use of statins but a causal attribution is more difficult to establish (Hippisley-Cox 2010; Smeeth 2008).

Our previous conclusion urging caution in the use of statins in people at low risk of cardiovascular events is no longer tenable in light of the CTT Collaboration findings. Several issues remain to be considered before widespread use of statins could be recommended in people at low risk (Ebrahim 2012; Smeeth 2012). These include: i) the feasibility and desirability of having to treat the majority of people over the age of 50 with a statin; ii) the cost-effectiveness of such a strategy using a conventional healthcare delivery system; iii) diversion of attention from achieving coverage in people at high risk of events; iv) use of alternative public health strategies to lower blood cholesterol; v) the views of patients on life-long drug therapy; and vi) limited evidence on less serious but nonetheless potentially important adverse effects and quality of life.

The National Institute for Health & Clinical Excellence UK (NICE) has provided some cost-effectiveness 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 Organization’s policy for CVD prevention (WHO 2008b).

Low cost generic statins are now widely available and recent cost-effectiveness studies show that statins are cost-saving in the USA even in people at low levels of predicted CHD risk. To gain maximal impact from using statins, 64 million people in the USA (just under half of the over 35 year old population) would need to be put on treatment at a cost of US\$2,800 per QALY gained (Lazar 2011). These cost-effectiveness estimates are likely to be better for more potent statins and in lower cost health services.

AUTHORS’ CONCLUSIONS

Implications for practice

The totality of evidence now supports the benefits of statins for primary prevention. The individual patient data meta-analyses now provide strong evidence to support their use in people at low risk of cardiovascular disease. Further cost-effectiveness analyses are now needed to guide widening their use to these low risk groups.

Implications for research

In addition to the cost-effectiveness analyses referred to above, it

will be useful to study the effects of public health interventions that attempt to alter diet and physical activity patterns and compare their effects with statins in robust randomised trials given recent evidence of large independent survival benefits of physical fitness in those taking statins in a large prospective cohort study (Kokkinos 2012). Relevant interventions might include nutrition education, exercise prescription, physical education curriculums that may be effective in changing lifestyle behaviours. (Jepson 2000) Studies of patient experiences and views on long-term use of statins are also needed to improve adherence to treatment. It is likely that further trials will be conducted in younger adults with adverse risk factor profiles which are associated with higher lifetime CVD risk (Berry 2012) and also in children (de Ferranti 2008). It is important that these trials examine comprehensively potential adverse effects of statins and quality of life, reporting on them in an unbiased way.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACAPS 1994

Methods	Randomised trial 4 x 4 factorial.
Participants	919 participants based in the USA aged 40 - 79 (mean age of 62); 52% men. None with any clinical evidence of CVD
Interventions	20 mg lovastatin + 1 mg warfarin versus placebo followed up for 34 months
Outcomes	Carotid atherosclerosis, cholesterol, fatal + non-fatal CHD events, stroke
Notes	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation stratified by centre
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Carers and patients were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT, no drop-outs reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

Adult Japanese MEGA Study

Methods	Randomised trial.
Participants	7832 participants with hypercholesterolaemia based in Japan aged 40-70 (mean age 59) ; 32% men. None with any clinical evidence of CVD
Interventions	10-20 mg pravastatin versus placebo; all participants got advice on diet; follow-up 5 years

Adult Japanese MEGA Study (Continued)

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	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation by permuted block method.
Allocation concealment (selection bias)	Low risk	Central laboratory.
Blinding (performance bias and detection bias) All outcomes	High risk	Single blinded, endpoint committee was blinded only because investigators stated that placebo-controlled trials are regarded with suspicion by Japanese participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used 2% dropped out.
Selective reporting (reporting bias)	High risk	Not all adverse events reported. We wrote to the authors asking for clarity regarding data on serious events. The authors responded saying they were unable to send the data
Other bias	Low risk	Groups were comparable at baseline and includes all the major prognostic factors Funded by pharmaceutical industry.

AFCAPS/TexCAPS 1998

Methods	Randomised trial.
Participants	6606 participants in Texas, USA; mean age 58; 57.5% men; 89% Caucasian. None with any clinical evidence of CVD
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 non-fatal 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 at 5.2 years

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Not described	
Allocation concealment (selection bias)	Unclear risk	Not described	
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel	
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used no drop-outs reported	
Selective reporting (reporting bias)	Low risk	Other than results for cholesterol	
Other bias	Unclear risk	Funded by pharmaceutical industry	

ASPEN 2006

Methods	Randomised trial.
Participants	2410 participants with type 2 diabetes based in 16 developed countries with mean age 60; 62.5% men; 84% Caucasian. < 10% with clinical evidence of CVD
Interventions	10 mg 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

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	Not described	
Allocation concealment (selection bias)	Unclear risk	Not described	

ASPEN 2006 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used 22% drop-outs reported
Selective reporting (reporting bias)	Low risk	Other than not providing results on adverse events for primary prevention group
Other bias	Unclear risk	Funded by pharmaceutical industry

Bone 2007

Methods	Randomised control trial.
Participants	626 Post-menopausal women aged 40-75 years with dyslipidaemia and no history of CHD or diabetes. None with any clinical evidence of CVD
Interventions	Atorvastatin (10/20/40/80 mg/day) with matching placebo. All patients were instructed to be on NCEP ATP III diet
Outcomes	Primary: Percentage change in lumbar spine bone marrow density Secondary: Percentage change in femoral neck etc BMD by DXA. other; adverse events
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated pseudo random code
Allocation concealment (selection bias)	Low risk	Random permuted blocks
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States double blind but only reported that participants were blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 5% dropped out.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Funded by pharmaceutical industry

CAIUS 1996

Methods	Randomised trial.
Participants	305 participants with hypercholesterolaemia based in Italy with mean age 55; 53% men. None with any clinical evidence of CVD
Interventions	40 mg pravastatin versus placebo; follow-up of three years.
Outcomes	Slope of carotid artery, fatal and non-fatal MI, angina, revascularisations, cholesterol and adverse events
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent co-ordinating centre controlled allocation
Allocation concealment (selection bias)	Low risk	Independent co-ordinating centre controlled allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 13% dropped out
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

CARDS 2008

Methods	Randomised control trial.
Participants	2838 participants with diabetes based in UK and Ireland aged 40-75 years (mean 61.7) ; 68% men; 94.5% Caucasian. None with any clinical evidence of CVD
Interventions	10 mg atorvastatin, all patients were given counselling on cessation of smoking; follow up of 3.9-4 years
Outcomes	Primary: composite of fatal and non-fatal 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

CARDS 2008 (Continued)

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code	
Allocation concealment (selection bias)	Low risk	Staff and patients unaware of computer-generated randomisation code	
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-blind: participants, personnel and outcome assessors	
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, no drop-outs reported	
Selective reporting (reporting bias)	Low risk		
Other bias	Unclear risk	Funded by pharmaceutical industry	

CELL A 1996

Methods	Randomised trial; 2 x 3 factorial design.
Participants	228 participants with hyperlipidaemia based in Sweden with a mean age of 49; 85% men, <10% had clinical evidence of CVD
Interventions	10-40 mg pravastatin plus intensive dietary advice versus placebo; follow-up for 18 months
Outcomes	Fatal MI, cholesterol, quality of life.
Notes	

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Not described	
Allocation concealment (selection bias)	Low risk	Randomisation performed separately for each centre with numbers allocated to intervention and control groups	

CELL A 1996 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 14.5% dropped out
Selective reporting (reporting bias)	High risk	Adverse events rates not provided for each group
Other bias	Unclear risk	Funded by pharmaceutical industry

CELL B 1996

Methods	Randomised trial; 2 x 3 factorial design.
Participants	227 participants with hyperlipidaemia based in Sweden with a mean age of 49; 85% men, <10% had clinical evidence of CVD
Interventions	10-40 mg pravastatin plus dietary advice versus placebo; follow-up for 18 months
Outcomes	Fatal MI, cholesterol, quality of life.
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation performed separately for each centre with numbers allocated to intervention and control groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 6% dropped out
Selective reporting (reporting bias)	Unclear risk	CVD and adverse events rates not provided for each group
Other bias	Unclear risk	Funded by pharmaceutical industry

CERDIA 2004

Methods	Parallel group randomised control trial.
Participants	250 patients with type 2 Diabetes aged 30-80 years. None with any clinical evidence of CVD
Interventions	0.4 mg of Cerivastatin until 08/2001 then Simvastain 20 mg.
Outcomes	Primary outcome: Change in mean common carotid intima media thickness (IMT) after 24 months of intervention. Secondary outcomes: Changes in Mean + maximum IMT at 24 months, CVD events, amputation due to atherosclerotic disease, serum levels of LDL and total cholesterol
Notes	In August 2001, Cerivstatin was withdrawn from market.

Risk of bias**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined computer-generated randomisation sequence in block of 10
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	States double blind but only reported that participants were blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT not used, 27% dropped out.
Selective reporting (reporting bias)	Low risk	States double blind but unclear who was blinded.
Other bias	Unclear risk	Comparable at baseline, including all major prognostic group however its unclear if it was valid and reliable method to determine outcomes Funded by pharmaceutical industry.

Derosa 2003

Methods	Randomised trial.
Participants	47 participants with hypercholesterolaemia based in Italy with a mean age of 51; 46% men. None with any clinical evidence of CVD
Interventions	80 mg fluvastatin versus placebo; all participants were given advice on diet and exercise ; follow-up for one year

Derosa 2003 (Continued)

Outcomes	Adverse events, cholesterol.	
Notes		
<i>Risk of bias</i>		
	<i>Risk of bias</i>	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Envelopes containing randomisation codes prepared by statistician
Allocation concealment (selection bias)	Low risk	Allocation code could only be identified by statistician and person responsible for statistical analysis
Blinding (performance bias and detection bias) All outcomes	Low risk	Single blind: participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, no drop-outs reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

HYRIM 2007

Methods	Randomised trial 2 x 2 factorial design.	
Participants	287 men with hypertension based in Norway aged 40-75 years (mean age 57). None with any clinical evidence of CVD	
Interventions	40 mg fluvastatin; follow-up four years.	
Outcomes	Primary: composite of fatal and non-fatal MI, + stroke, angina, sudden CHD death, TIA and heart failure. MACE: composite of cardiac death, fatal and non-fatal MI and revascularisation. Single outcomes included: adverse events, cholesterol	
Notes		
<i>Risk of bias</i>		
	<i>Risk of bias</i>	
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

HYRIM 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described and no drop-outs reported
Selective reporting (reporting bias)	Low risk	Mostly but not for adverse events and cholesterol level at baseline and at 4-year follow-up not provided
Other bias	Unclear risk	Groups comparable at baseline, including all major prognostic factors, structured interview for outcomes and side effects confirmed by independent expert committee Funded by pharmaceutical industry.

JUPITER 2008

Methods	Randomised control trial.
Participants	17,802 participants (intervention:8901, control 8901) > 50 years. None with any clinical evidence of CVD
Interventions	Rosuvastatin 20 mg daily.
Outcomes	First occurrence of major cardiovascular event, revascularisation, hospital admission for angina, MI, stroke, all-cause death, CVD death and adverse events
Notes	Stopped early with a follow-up of 1.9 years.

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done in block of 4, use of Interactive voice response system-generated allocation sequence
Allocation concealment (selection bias)	Low risk	Stratified according to the centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, participants and outcomes assessed by end point committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, no drop-outs reported

JUPITER 2008 (Continued)

Selective reporting (reporting bias)	Low risk	There was limited data on LDL and TC at the end of trial
Other bias	High risk	Groups comparable at baseline, including all major prognostic factors, structured interview assessing outcomes and adverse effects confirmed by independent expert committee. Trial was stopped early with a follow-up of 1.9 years. Funded by pharmaceutical industry

KAPS 1995

Methods	Randomised trial.
Participants	447 men based in Finland aged 44-65 years (mean 57). < 10% with clinical evidence of CVD
Interventions	40 mg 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	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Biostatistician prepared randomisation scheme
Allocation concealment (selection bias)	Low risk	Tablets were masked by pharmaceutical company
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT was not used, 17% patients dropped out
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

METEOR 2010

Methods	Randomised control trial.
Participants	984 asymptomatic individuals with a mean age of 57 years. None with any clinical evidence of CVD
Interventions	Rosuvastatin 40 mg/ day.
Outcomes	Primary: Mean of 12 Carotid Intima media (CIMT) thickness measurements. Secondary: CIMT measurements of left and right common carotid artery. Other relevant outcomes: adverse events, cholesterol levels
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in block of 7 (5 to intervention and 5 to control)
Allocation concealment (selection bias)	Low risk	Blinded study medication
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding both to participants and personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used 25-6% dropped out.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

MRC/BHF Heart Protection

Methods	Randomised trial (2 x 2 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	40 mg 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

Risk of bias

MRC/BHF Heart Protection (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described
Allocation concealment (selection bias)	Low risk	Central telephone system used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: participants and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	Only CVD event results provided for this subgroup
Other bias	Unclear risk	Funded by pharmaceutical industry.

PHYLLIS 2004

Methods	Randomised trial 4 x 4 factorial.
Participants	253 men and women aged 45-70 (mean age 58) with hypertension, hypercholesterolaemia and asymptomatic carotid atherosclerosis based in Italy. None with any clinical evidence of CVD
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			Risk of bias
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated in blocks of 4	
Allocation concealment (selection bias)	Unclear risk	Not described	
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind	

PHYLLIS 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 20% drop-outs reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

PREVEND IT 2004

Methods	Randomised trial 2 x 2 factorial design.
Participants	864 participants with microalbuminuria based in Holland aged 28-75 years (mean age 51); 64.5% men; 96% Caucasian. < 10% with clinical evidence of CVD
Interventions	40 mg 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, non-fatal MI and cholesterol
Notes	

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated.
Allocation concealment (selection bias)	Low risk	Participants randomised were allocated to a treatment number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT used but confined to CVD events, 6% dropped out
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

WOSCOPS

Methods	Randomised trial.
Participants	6595 men with hypercholesterolaemia based in Scotland aged 45-64 (mean age 55). < 10% with clinical evidence of CVD
Interventions	40 mg 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	

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of random numbers and treatment assigned randomly
Allocation concealment (selection bias)	Low risk	All trial personnel remained unaware of the participant's treatment assignment throughout the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 30% drop-outs reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

BMD: bone mineral density
 CHD: coronary heart disease
 CIMT: carotid intima media thickness
 CVD: cardiovascular disease
 DXA: Dual-energy X-ray absorptiometry
 ITT: intention-to-treat
 LDL: low density lipoprotein
 MI: myocardial infarction
 TC: total cholesterol
 TIA: transient ischaemic attack

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

Study	Reason for exclusion
Agewall 2006	Treatment length was less than a year
ALLHAT-LLT 2002	15% patients had history of CVD
Ames 2011	No relevant outcomes reported
Anderson 1993	No placebo - statin + antioxidant versus statin + antioxidant
ASCOT-LLA 2003	18% patients had history of CVD
ASTRONOMER 2010	Study is not a primary prevention
Bak 1998	Treatment length was less than a year
BCAPS 2001	11% patients had history of CVD
Bocuzzi 1991	Not a RCT - all participants were given Simvastatin
Branchi 1995	Control Group was not randomised
Byington 1993	Secondary prevention
CASHMERE 2007	Treatment length was less than a year
Cassader 1993	Treatment length was less than a year
CHALLENGER	Patients with CHD were included in study
Chan 1996	Treatment length was less than a year
Chuengsamarn 2010	Study is not a RCT
CLIP 2002	Not a RCT - All participants were given Pravastatin
Cowan 2010	Follow-up duration was inadequate
Coylewright 2008	Secondary prevention
CRISP 1994	Treatment length was less than a year
CURVES 1998	No placebo - statin versus statin
Dangas 1999	Treatment length was less than a year

(Continued)

Davidson 1997	No placebo - statin versus statin
Duffy 2001	Treatment length was less than a year
Egashira 1994	Not a RCT - All participants were given Pravastatin
Eriksson 1998	No control group - Pravastatin vs. Cholestyramine
EXCEL 1990	Treatment length was less than a year
Faergeman 2009	Comparison of two statins/doses
FAST 2002	Over 40% had CVD and over 14% had CHD
Ferrari 1993	Treatment length was less than a year
Gentile 2000	Treatment length was only 24 weeks
Glasser 1996	Length of treatment was only 12 weeks
Gomez-Garcia 2007	Follow-up period was less than a year
Guisasola 2009	Study is not a RCT
Hokuriku NK-104 Study 02	Not a RCT - All participants were given intravasating
Hongo 2010	No placebo control group
Hufnagel 2000	Treatment length was less than a year
Italian Family Physician	Not a RCT - open-labelled
J-LIT 2007	Study is not a RCT
Jardine 2006	Outcomes provided were aggregated. Unable to ascertain actual numbers for cardiac death and myocardial infarction
JART 2011	Comparison was between two types of statin
JELIS 2009	No placebo/control group and study was a secondary prevention
Jones 1991	Treatment length was less than a year
Kappelle 2009	Treatment length was less than a year
KLIS 2000	Not randomised

(Continued)

Kojima 2010	Secondary prevention
Lemaitre 2002	Cohort study
Lin 2010	No relevant outcomes reported.
LIPID 2010	Secondary prevention
Mareev 2008	Previous history of cardiovascular disease in most patients
McDermott 2003	Participants were not randomised to statins or no statins
Mizuguchi 2008	Study outcomes are not relevant to current review.
Mohler 2003	Patients recruited had peripheral arterial disease
Mok 2009	Secondary prevention
Muldoon 1997	Treatment length is only six months
Nephrotic Syndrome Study	Treatment length was less than a year
Ohta 2000	Treatment length was less than a year
Oi 1997	No placebo or control group
Olzowy 2007	Outcomes of the study are not relevant to review.
Ormiston 2003	Not a RCT - all participants were given statins
Pavia 2000	Intervention included Amlodipine
Pitt 1999	No placebo - statins versus angioplasty
POSCH 1990	Statins were not used
Pravastatin Multi 1993	Treatment length was less than a year
PROSPER 2002	More than 10% of the participants had CVD
Safaei 2007	Study is not a RCT
SANDS 2008	Comparison of two different treatment algorithms which included statins
Schmermund 2006	Comparision of 10 mg vs 80 mg of statin.

(Continued)

Sen 2000	Treatment length was less than a year
Sprecher 1994	Treatment length was less than a year
Stein 1997	Treatment length was less than a year
Su 2000	Treatment length was less than a year
Tanaka 2001	Treatment length was less than a year
Tarin 2010	Secondary prevention
Teixeira 2011	No relevant outcomes
Tekin 2008	Not randomised
Thomas 1993	Treatment length was less than a year
Thrombosis Prevention	Statins were not used
Togha 2009	Patients had a chronic disease.
Tran 2007	The data are based on inadequate length of treatment
Wallace 2003	Treatment length was less than a year
Wu 2007	No comparison group
Yu-An 1998	Treatment length was less than one year
Zachoval 2000	Comparison of two statins

CHD: coronary heart disease

CVD: cardiovascular disease

RCT: randomised controlled trial

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

Babes 2010

Methods	RCT
Participants	Young adults
Interventions	Statin

Babes 2010 (Continued)

Outcomes	Endothelial dysfunction
Notes	We wrote on three separate occasions to the authors for further information on this study and did not receive a response

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Mortality and Morbidity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Mortality	13	48060	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
2 Total Number of CHD Events	14	48049	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.67, 0.80]
3 Number of Fatal CHD Events	10	46094	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.96]
4 Number of Non-fatal CHD Events	11	40977	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.59, 0.76]
5 Total Number of CVD Events	9	23805	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.70, 0.81]
6 Number of Fatal CVD Events	5	34012	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]
7 Number of Non-fatal CVD Events	2	8696	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
8 Total Number of Stroke Events	10	40295	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]
9 Number of Fatal Stroke Events	3	27238	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.18, 2.23]
10 Number of Non-fatal Stroke Events	5	28097	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.58, 0.83]
11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events	4	35254	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.58, 0.73]
12 Number of Study Participants who underwent Revascularisation	7	42403	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.72]

Comparison 2. Lipids (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Cholesterol (mmol/L)	14	34122	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.35, -0.76]
2 LDL Cholesterol (mmol/L)	16	41380	Mean Difference (IV, Random, 95% CI)	-1.00 [-1.16, -0.85]

Comparison 3. Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of study participants who had adverse events	12	40716	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
2 Number of study participants who stopped treatment due to adverse events	9	21642	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.12]

3 Number of study participants who were admitted to hospital	2	19707	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.41]
4 Number of study participants who developed cancer	11	38739	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.10]
5 Number of study participants who developed myalgia or muscle pain	9	37938	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.97, 1.09]
6 Number of study participants who developed rhabdomyolysis	6	38468	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.23, 4.38]
7 Number of study participants who developed diabetes	2	24407	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [1.01, 1.39]
8 Number of study participants who developed haemorrhagic stroke	2	25634	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.54, 1.75]
9 Number of study participants who had elevated liver enzymes	10	40094	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.87, 1.54]
10 Number of study participants who developed renal disorder	4	27804	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.99, 1.26]
11 Number of study participants who developed arthritis	2	7586	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.82, 1.75]

Comparison 4. Treatment Compliance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment Compliance	8	41712	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.98, 1.18]

Comparison 5. Sensitivity Analysis

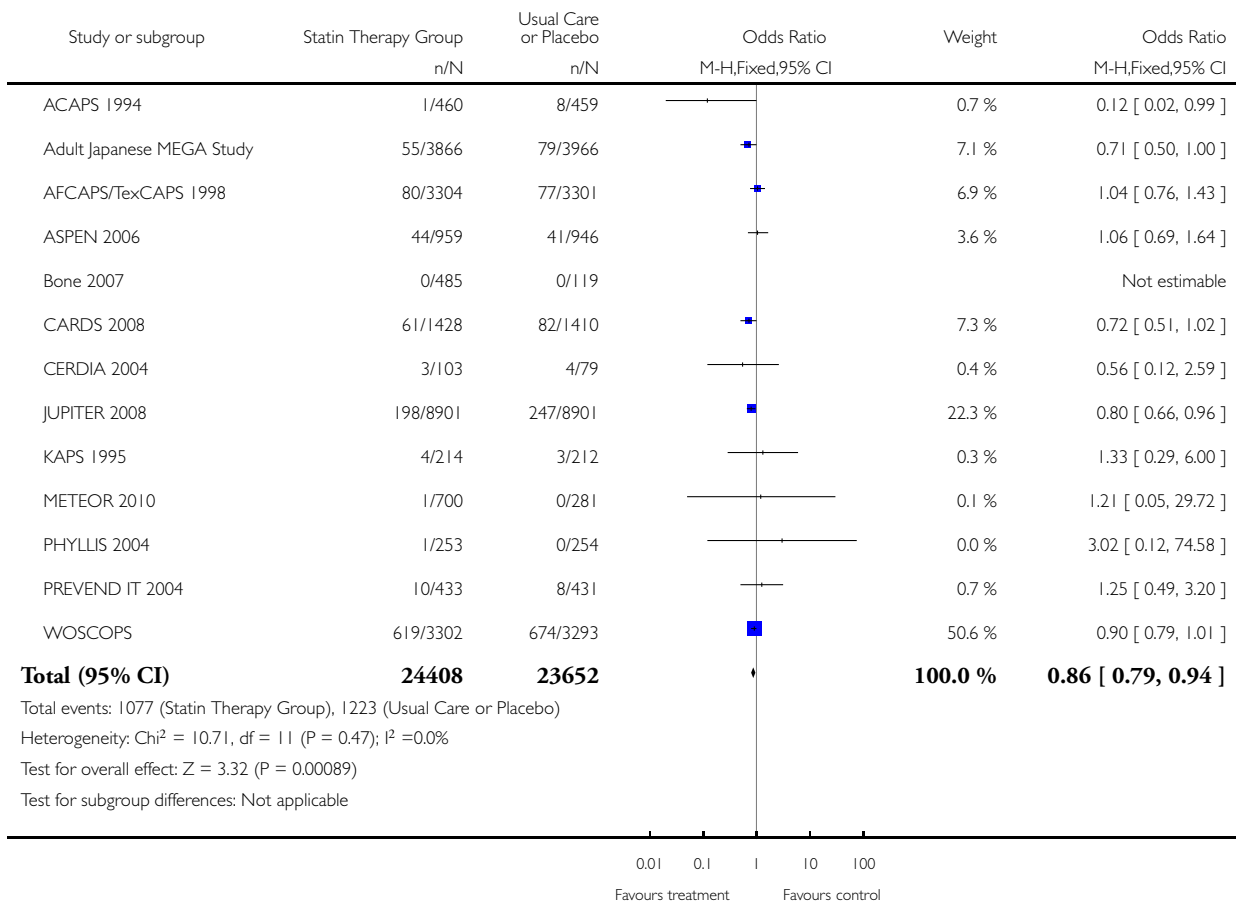
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early stopping of trials and total mortality	11	46811	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.74, 0.92]
1.1 trials stopped early	3	27245	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]
1.2 trials with no early stop	8	19566	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
2 Early stopping of trials and total CHD events	14	48066	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.67, 0.80]
2.1 trials stopped early	3	27265	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.58, 0.79]
2.2 trials with no early stop	11	20801	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.69, 0.84]
3 Study Size for total Mortality	11	46811	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.74, 0.92]
3.1 Over 1000 participants	6	43754	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.92]
3.2 Under 1000 participants	5	3057	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.82]
4 Study Size for total CHD events	14	48066	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.67, 0.80]
4.1 Over 1000 participants	6	43597	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.67, 0.80]

Analysis 1.1. Comparison 1 Mortality and Morbidity, Outcome 1 Total Mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 1 Total Mortality

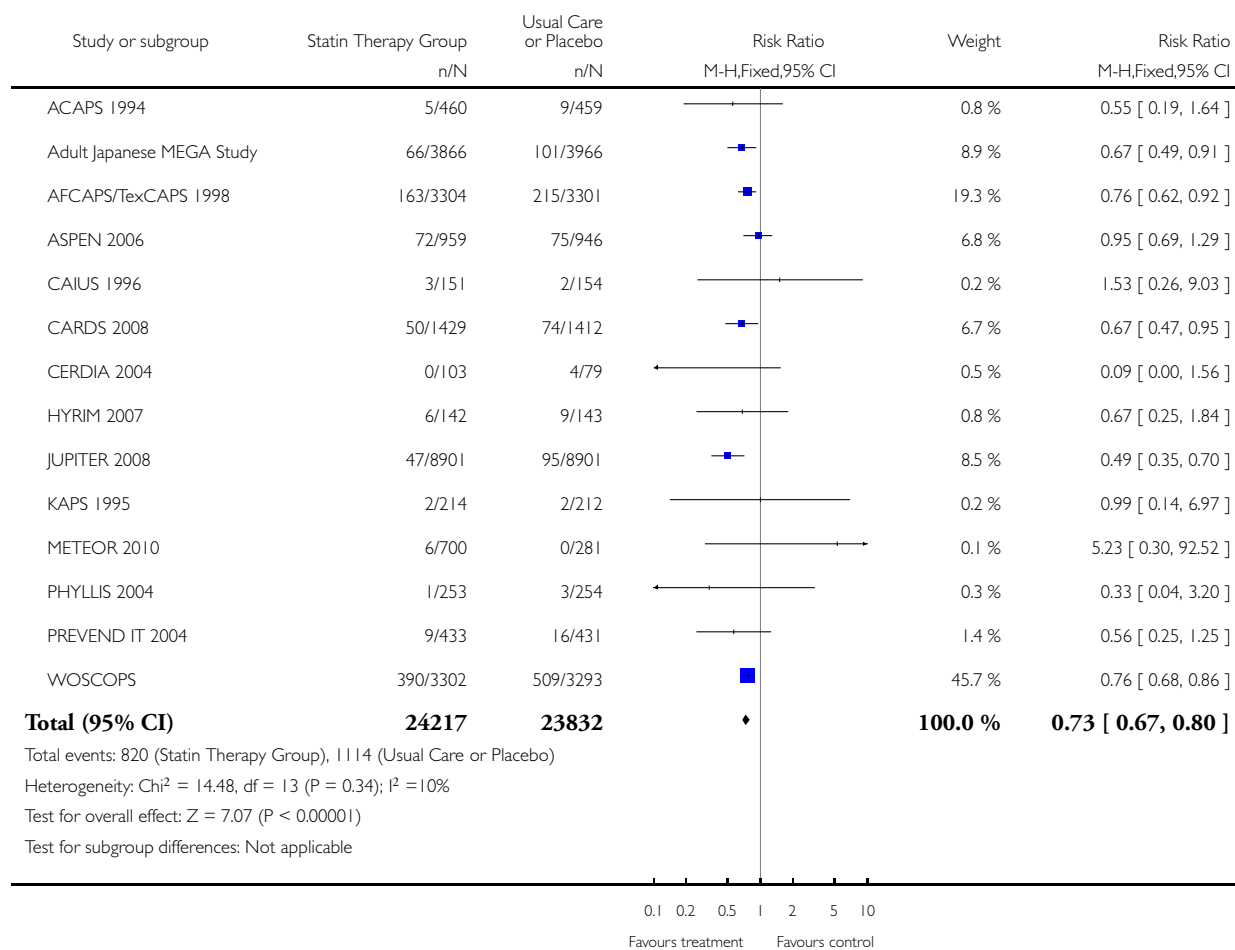


Analysis 1.2. Comparison 1 Mortality and Morbidity, Outcome 2 Total Number of CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 2 Total Number of CHD Events

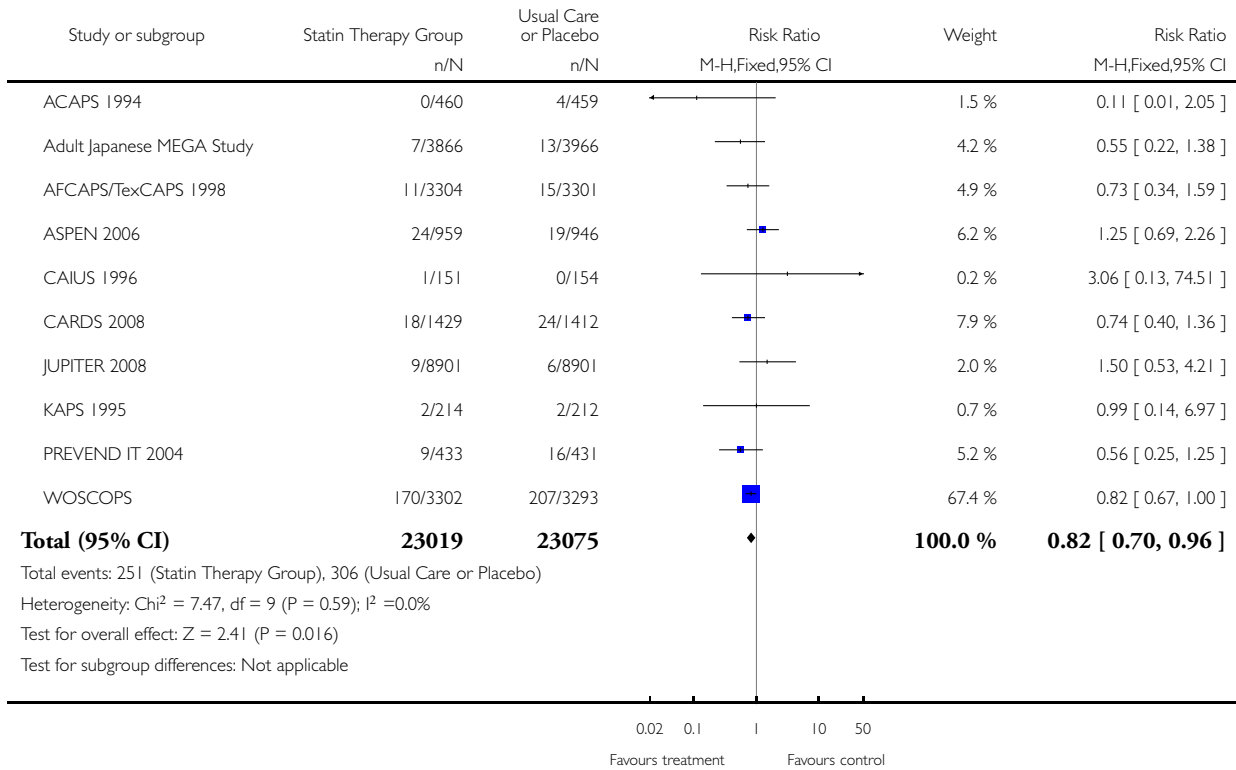


Analysis 1.3. Comparison 1 Mortality and Morbidity, Outcome 3 Number of Fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 3 Number of Fatal CHD Events

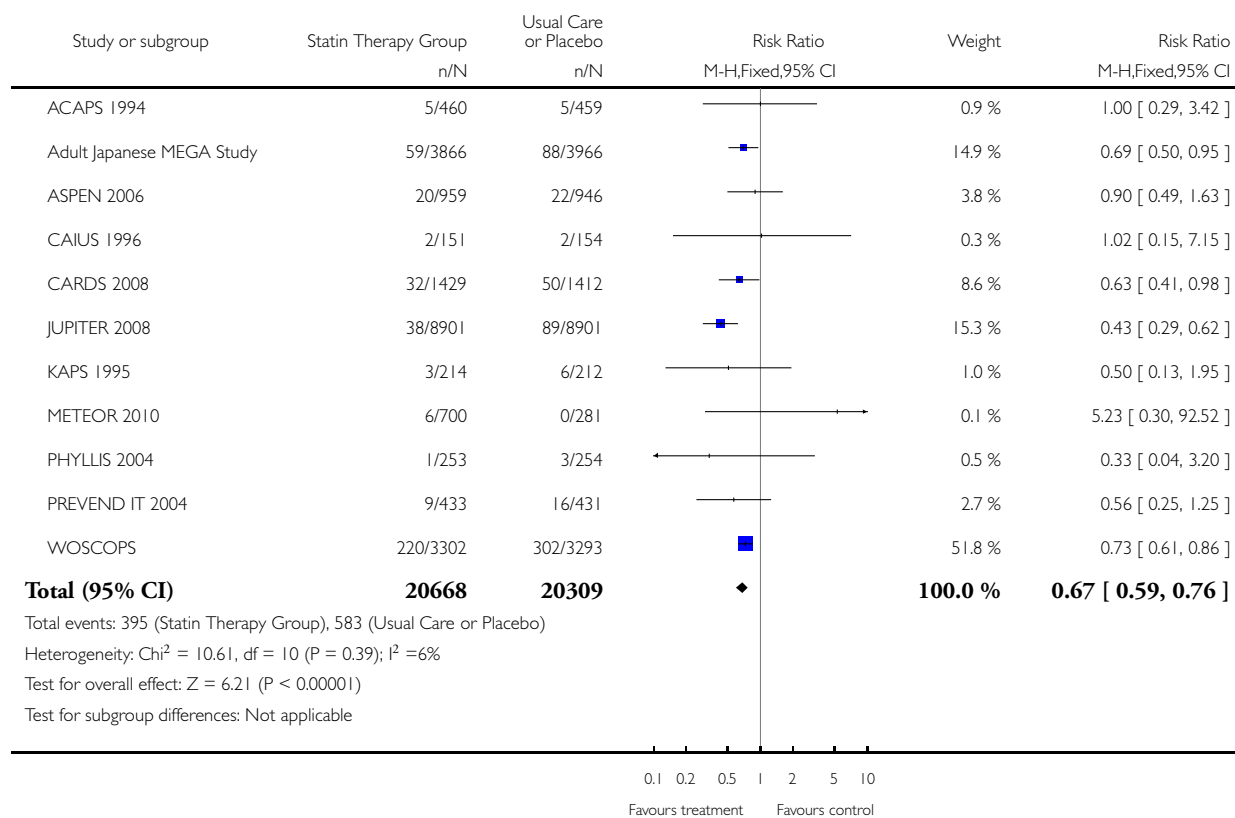


Analysis 1.4. Comparison 1 Mortality and Morbidity, Outcome 4 Number of Non-fatal CHD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 4 Number of Non-fatal CHD Events

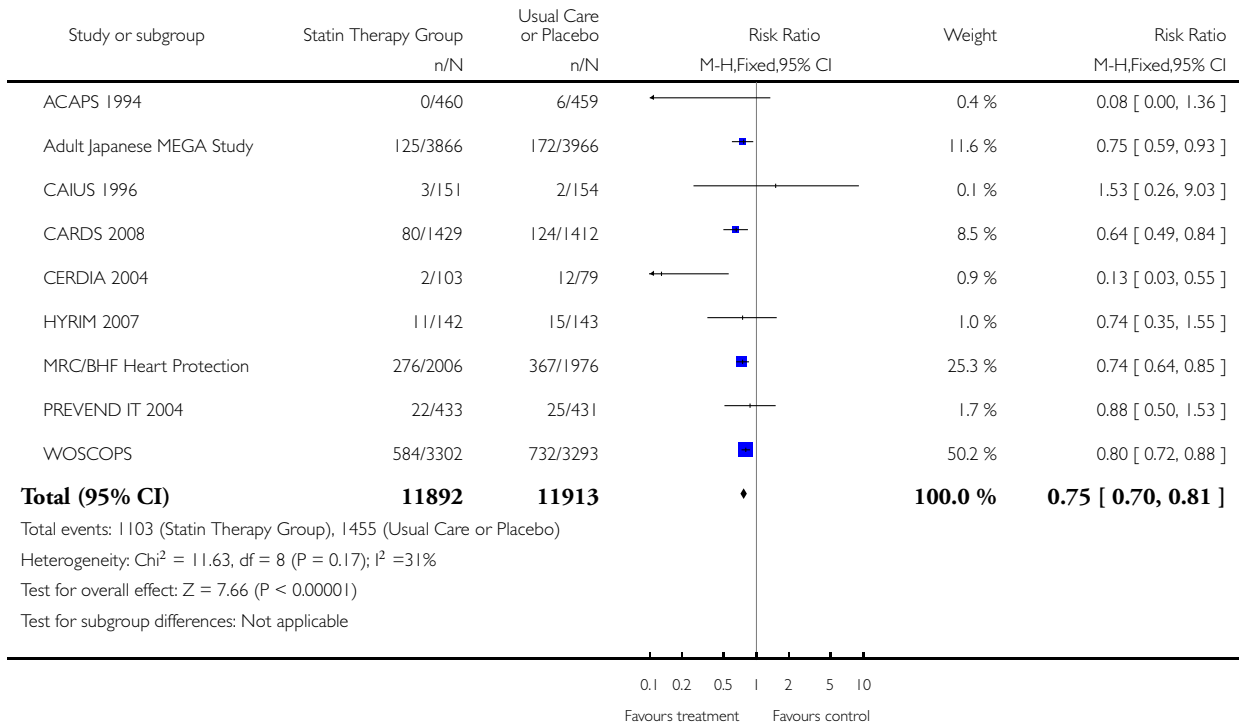


Analysis 1.5. Comparison 1 Mortality and Morbidity, Outcome 5 Total Number of CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 5 Total Number of CVD Events

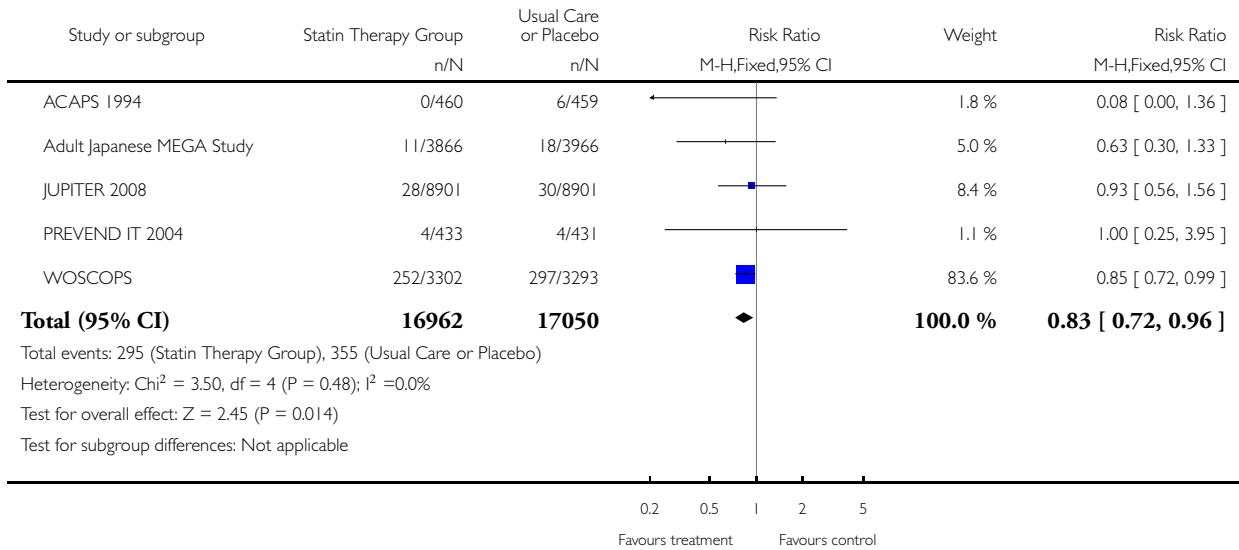


Analysis 1.6. Comparison 1 Mortality and Morbidity, Outcome 6 Number of Fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 6 Number of Fatal CVD Events

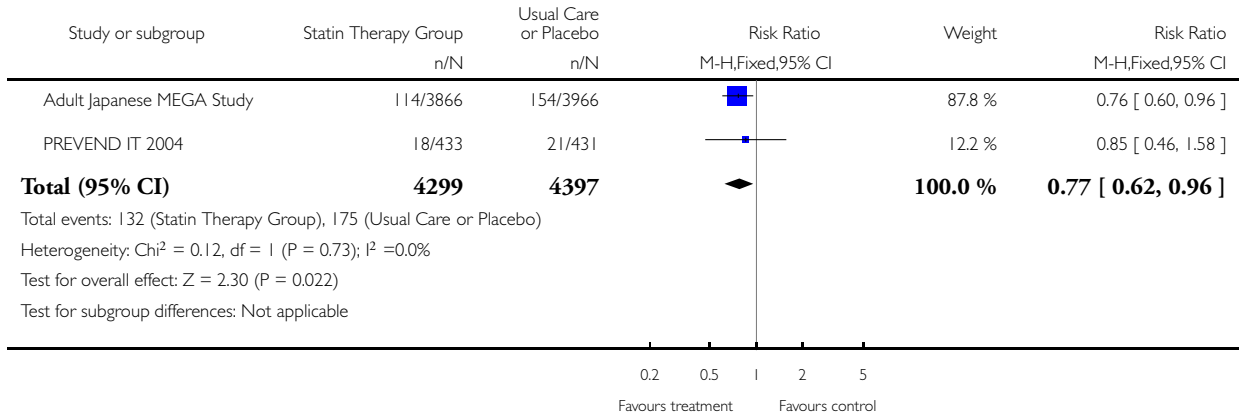


Analysis 1.7. Comparison 1 Mortality and Morbidity, Outcome 7 Number of Non-fatal CVD Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 7 Number of Non-fatal CVD Events

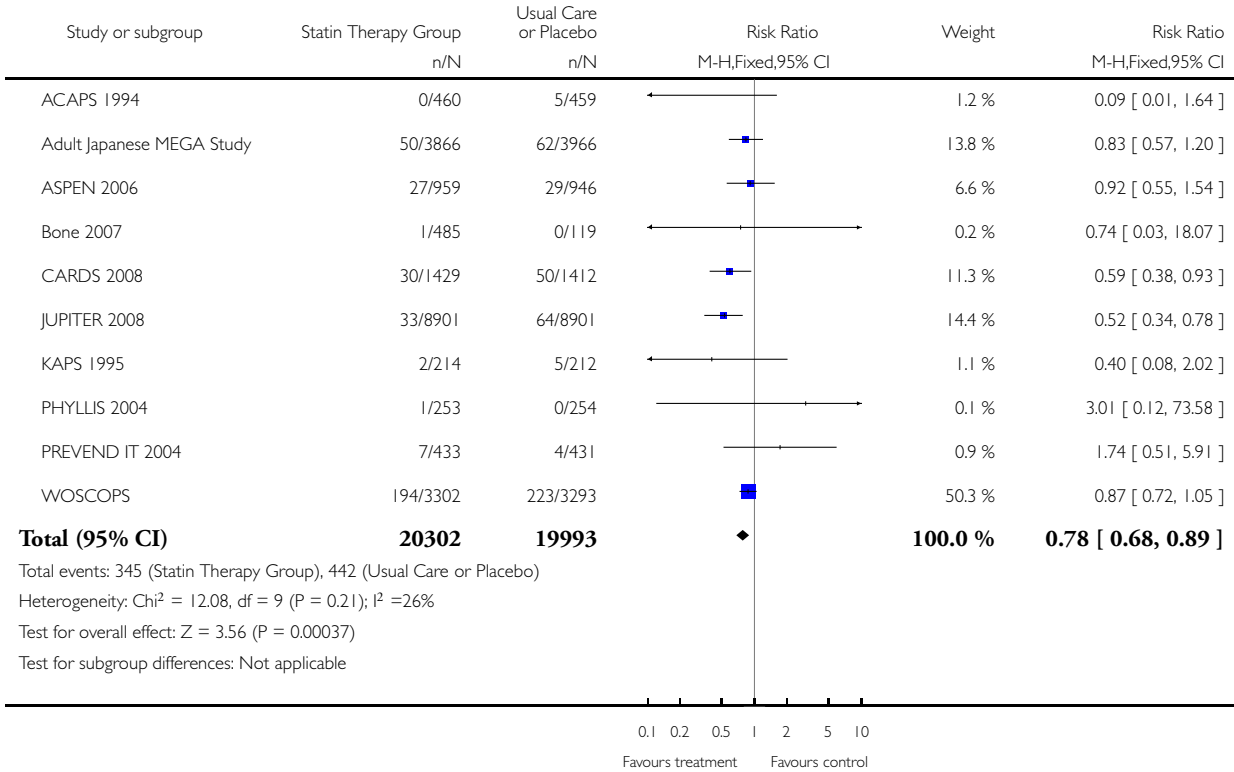


Analysis 1.8. Comparison 1 Mortality and Morbidity, Outcome 8 Total Number of Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 8 Total Number of Stroke Events

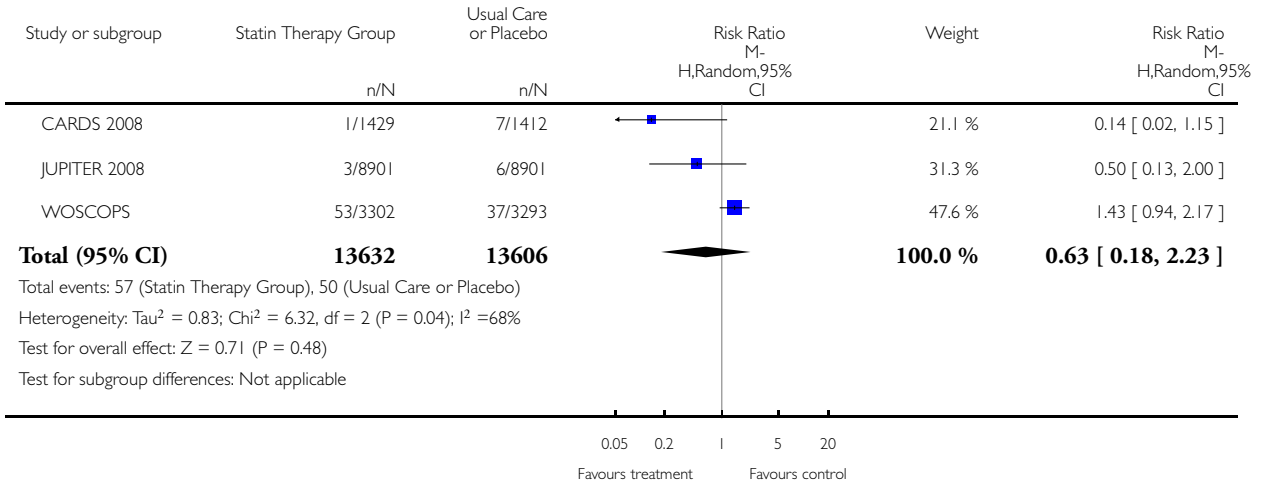


Analysis 1.9. Comparison 1 Mortality and Morbidity, Outcome 9 Number of Fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 9 Number of Fatal Stroke Events

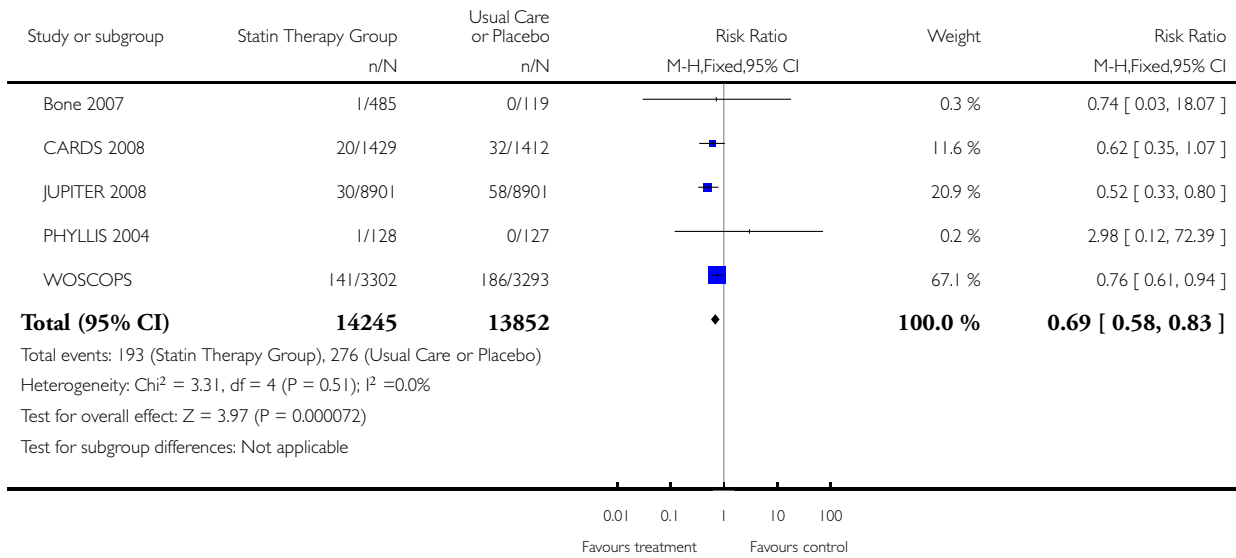


Analysis 1.10. Comparison 1 Mortality and Morbidity, Outcome 10 Number of Non-fatal Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 10 Number of Non-fatal Stroke Events

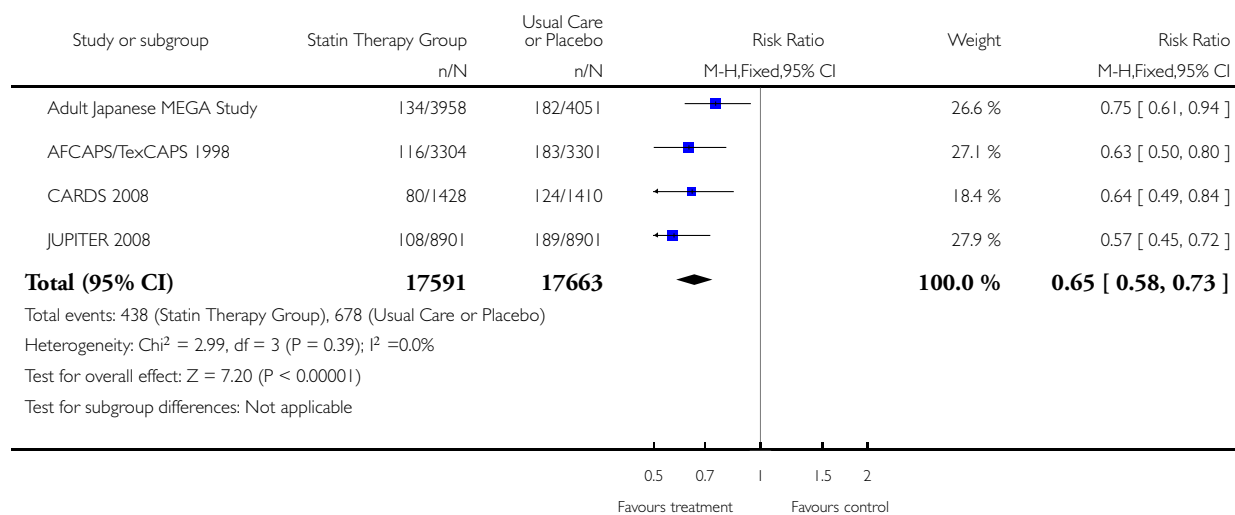


Analysis 1.11. Comparison 1 Mortality and Morbidity, Outcome 11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

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

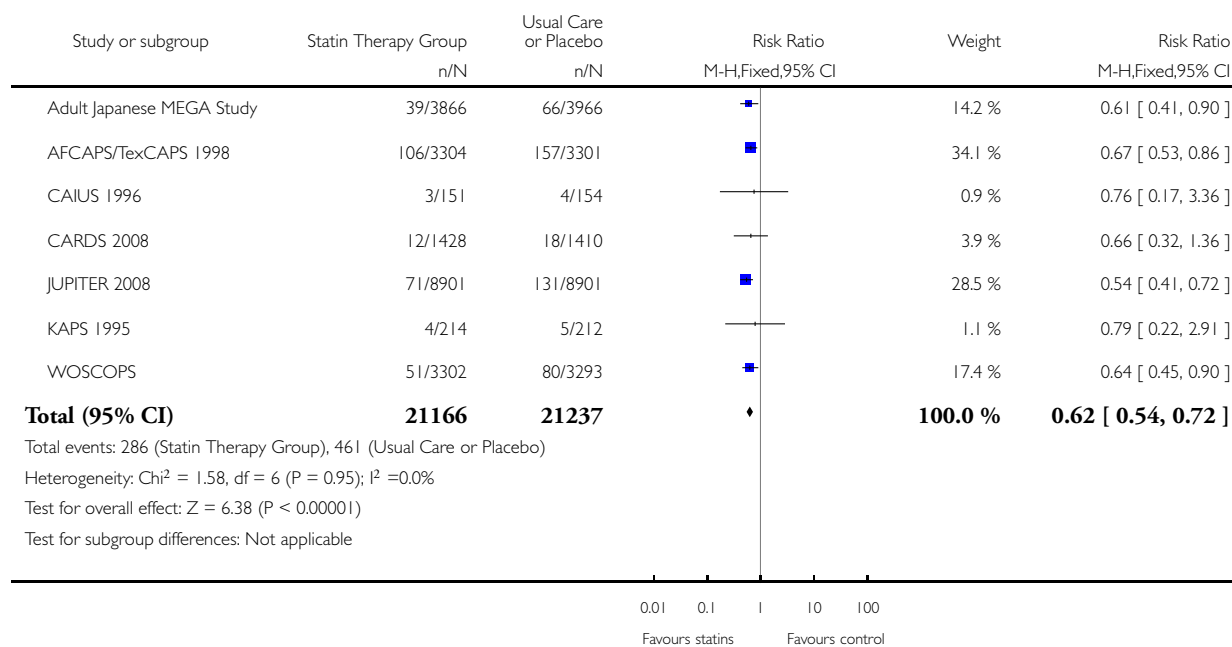


Analysis 1.12. Comparison 1 Mortality and Morbidity, Outcome 12 Number of Study Participants who underwent Revascularisation.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 12 Number of Study Participants who underwent Revascularisation

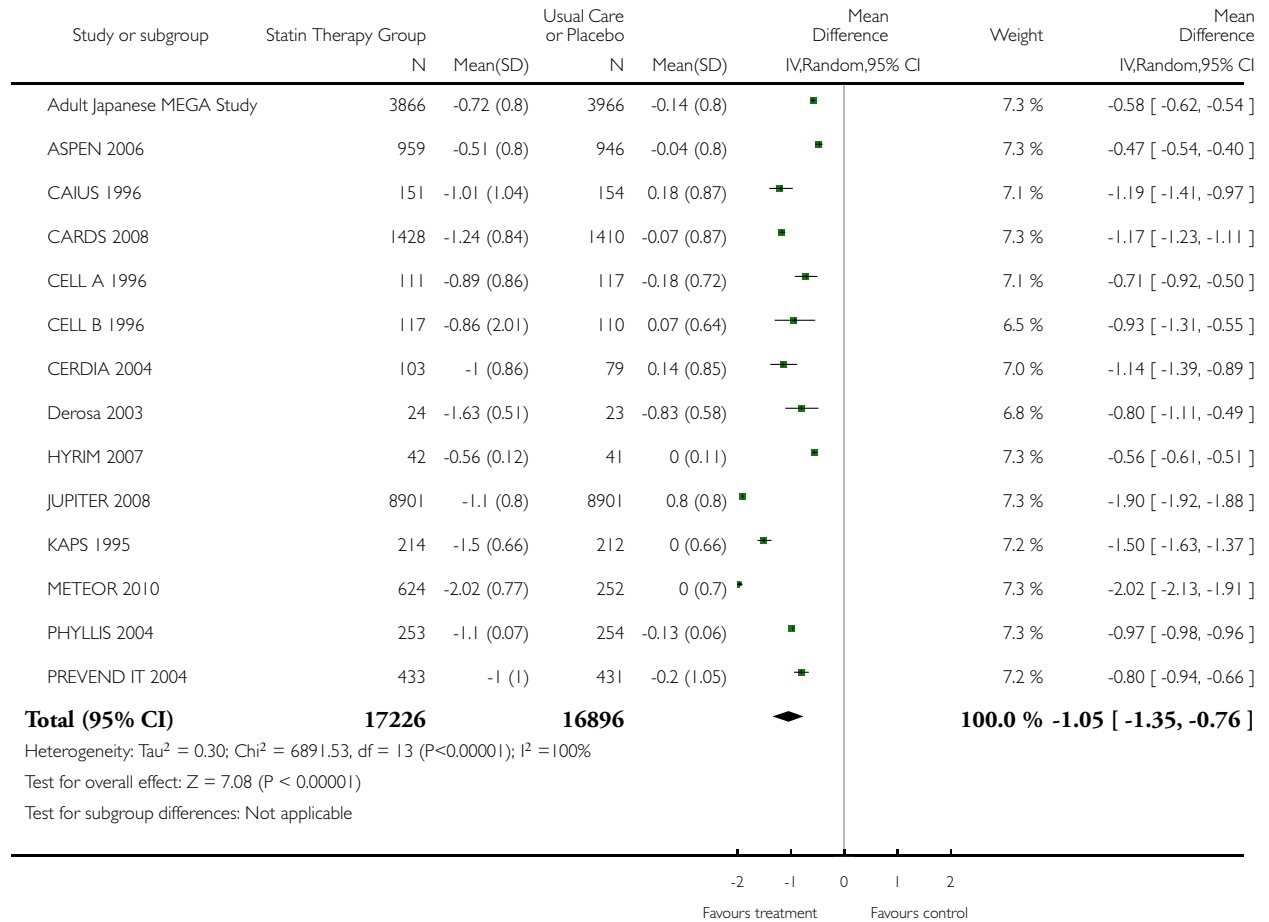


Analysis 2.1. Comparison 2 Lipids (mmol/L), Outcome 1 Total Cholesterol (mmol/L).

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Lipids (mmol/L)

Outcome: 1 Total Cholesterol (mmol/L)

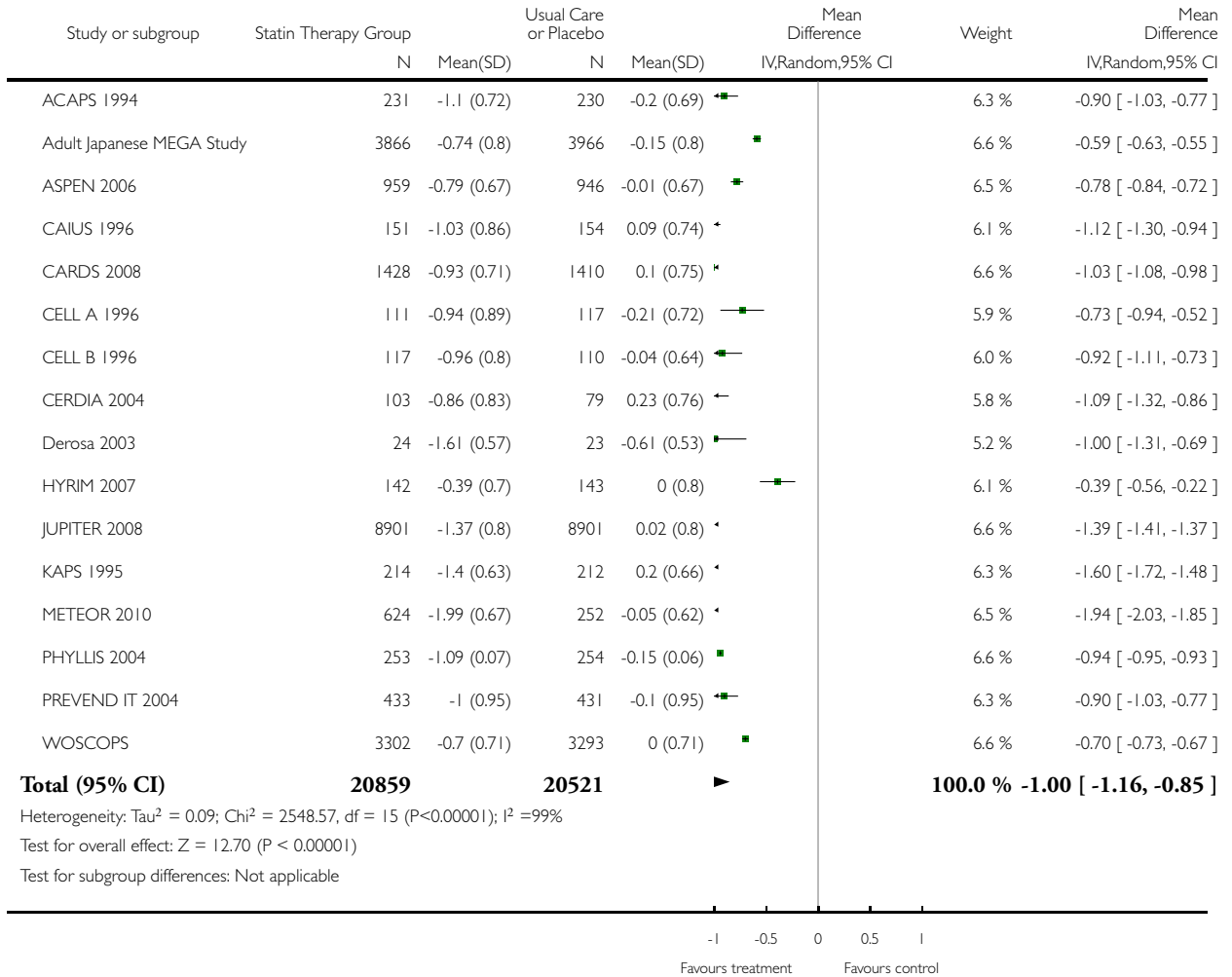


Analysis 2.2. Comparison 2 Lipids (mmol/L), Outcome 2 LDL Cholesterol (mmol/L).

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 2 Lipids (mmol/L)

Outcome: 2 LDL Cholesterol (mmol/L)

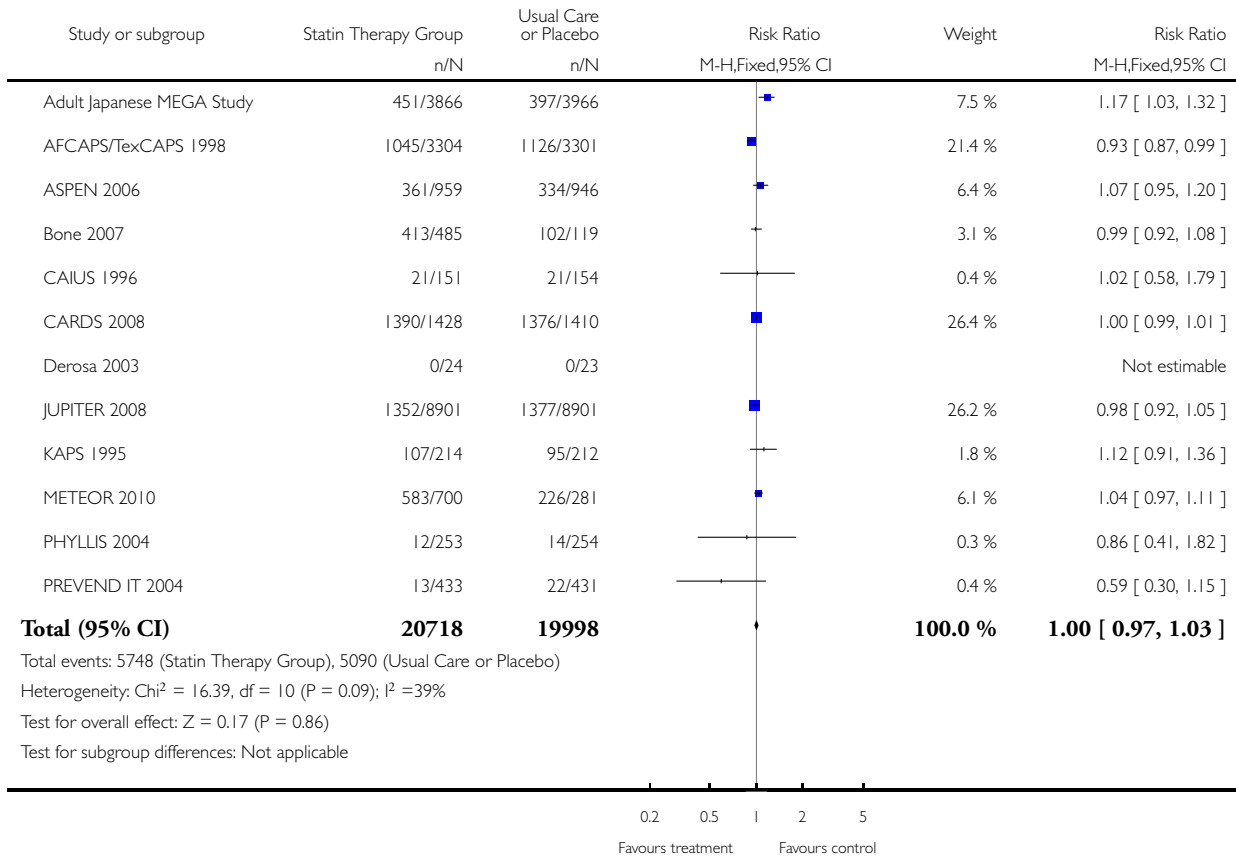


Analysis 3.1. Comparison 3 Adverse Events, Outcome 1 Number of study participants who had adverse events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 1 Number of study participants who had adverse events

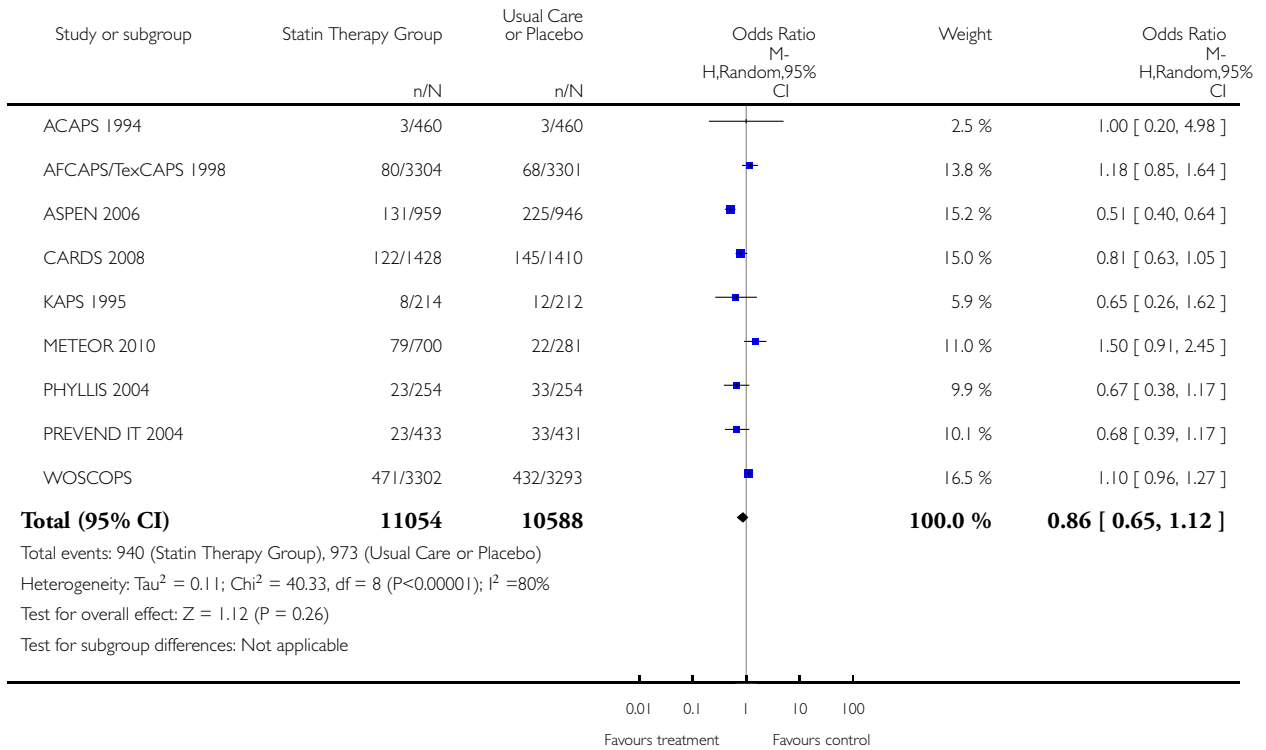


Analysis 3.2. Comparison 3 Adverse Events, Outcome 2 Number of study participants who stopped treatment due to adverse events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 2 Number of study participants who stopped treatment due to adverse events

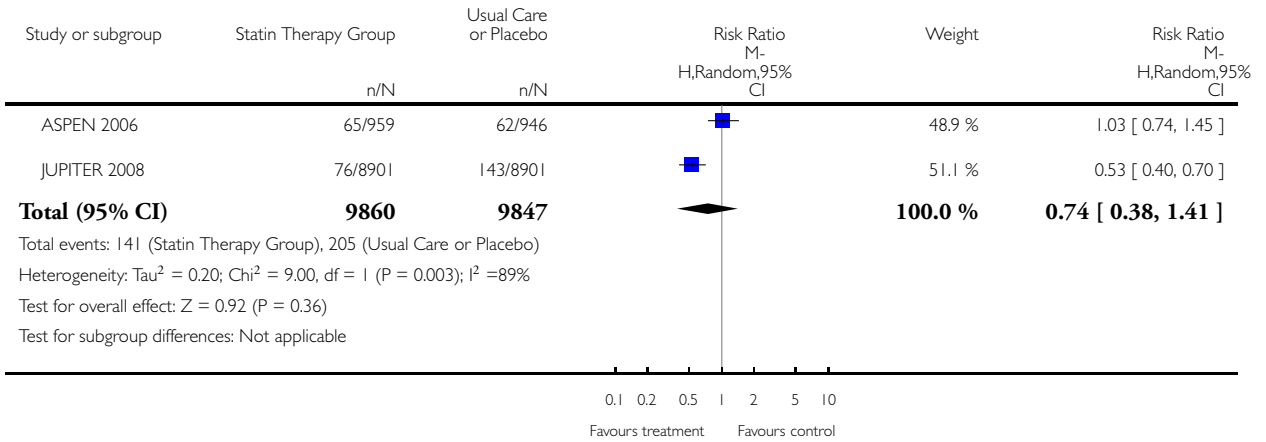


Analysis 3.3. Comparison 3 Adverse Events, Outcome 3 Number of study participants who were admitted to hospital.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 3 Number of study participants who were admitted to hospital

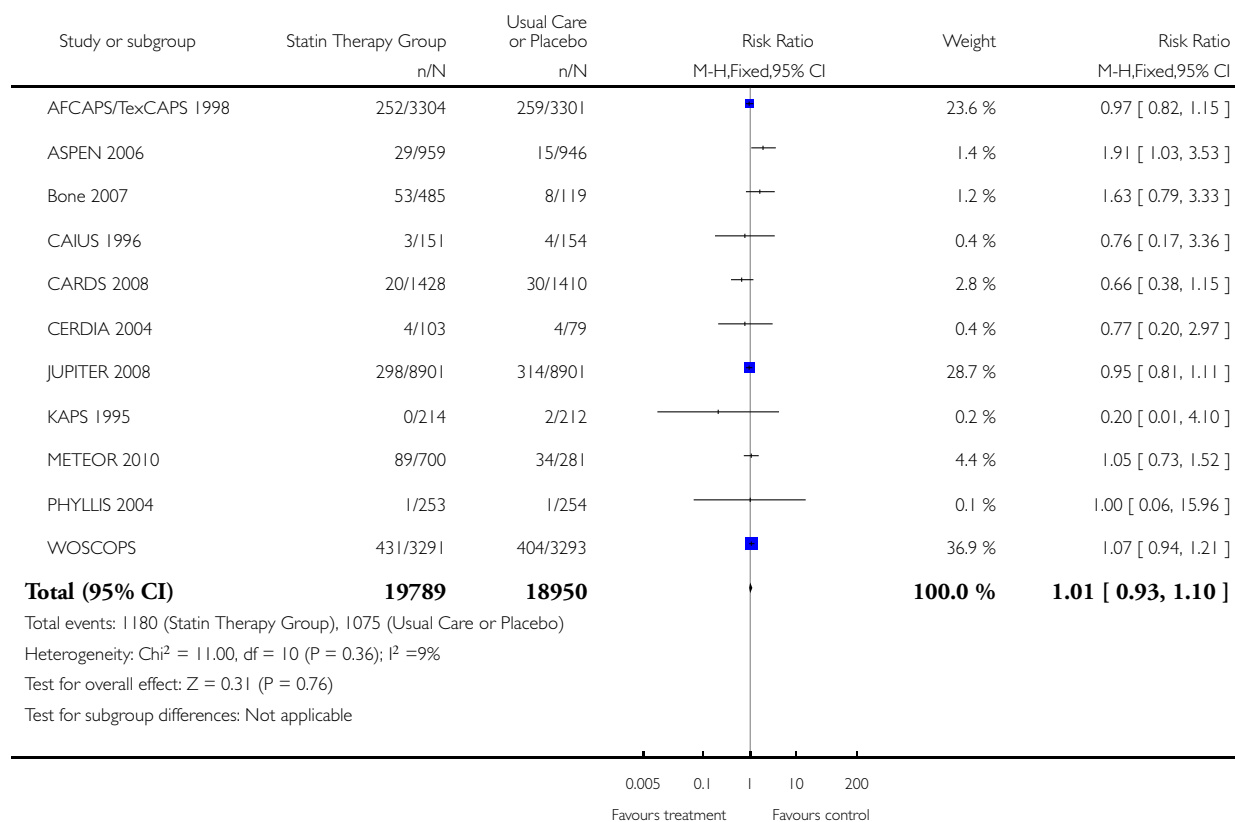


Analysis 3.4. Comparison 3 Adverse Events, Outcome 4 Number of study participants who developed cancer.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 4 Number of study participants who developed cancer

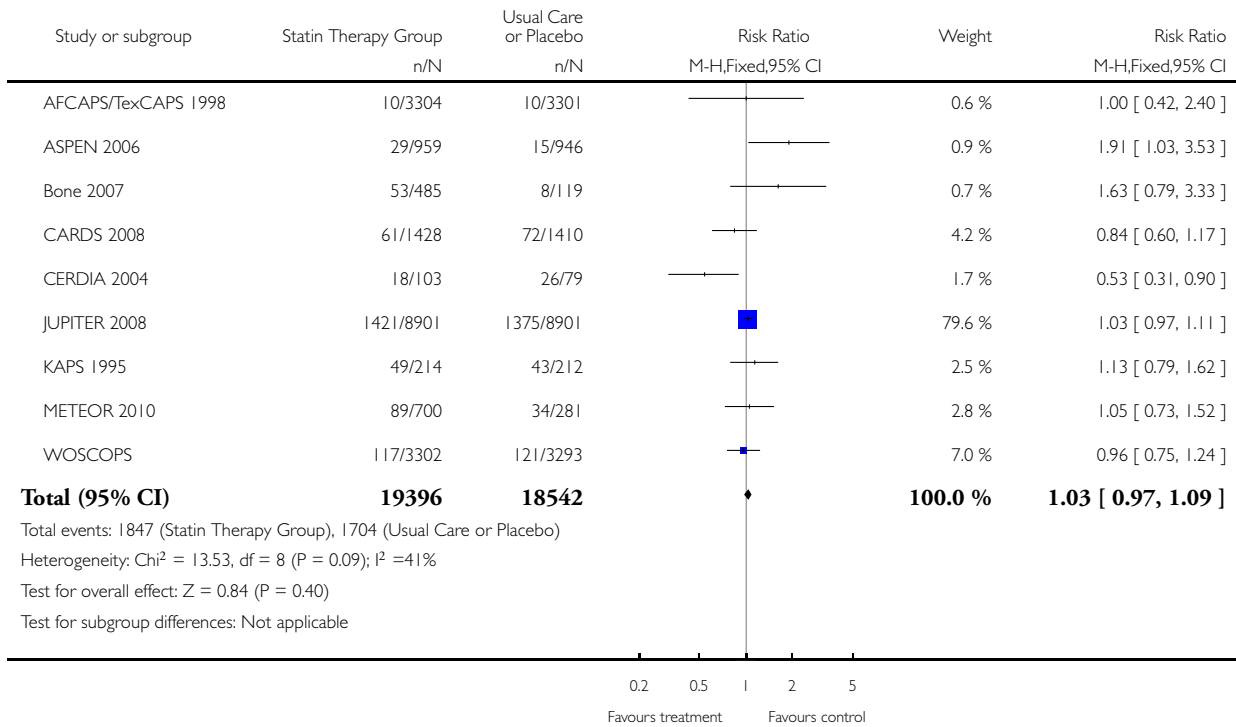


Analysis 3.5. Comparison 3 Adverse Events, Outcome 5 Number of study participants who developed myalgia or muscle pain.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 5 Number of study participants who developed myalgia or muscle pain

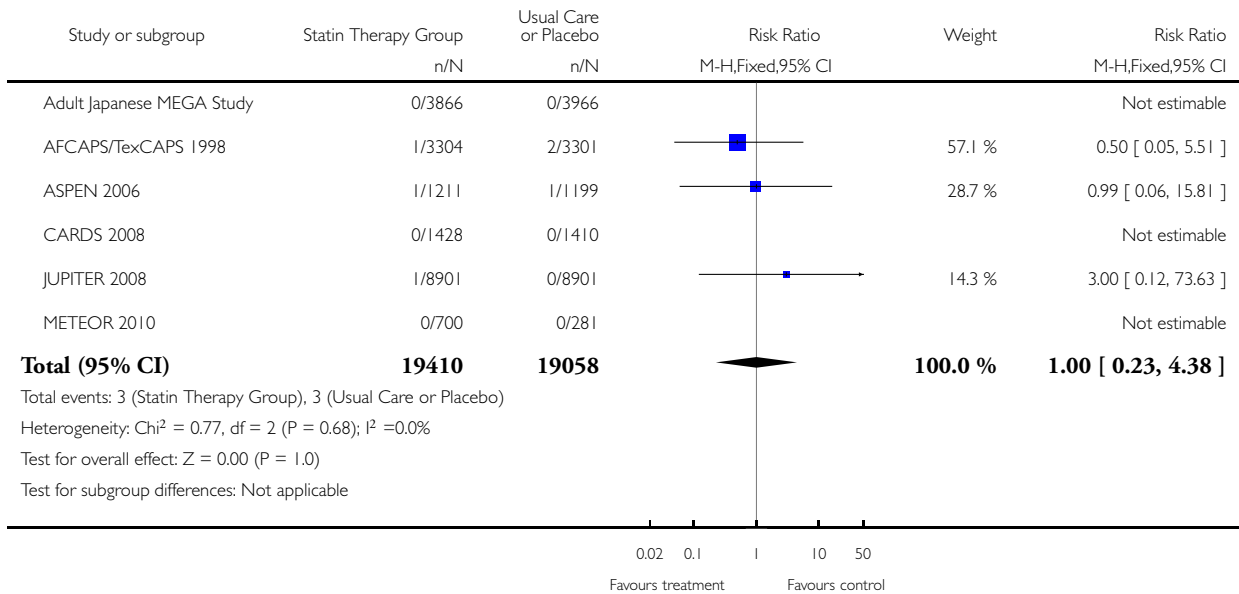


Analysis 3.6. Comparison 3 Adverse Events, Outcome 6 Number of study participants who developed rhabdomyolysis.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 6 Number of study participants who developed rhabdomyolysis

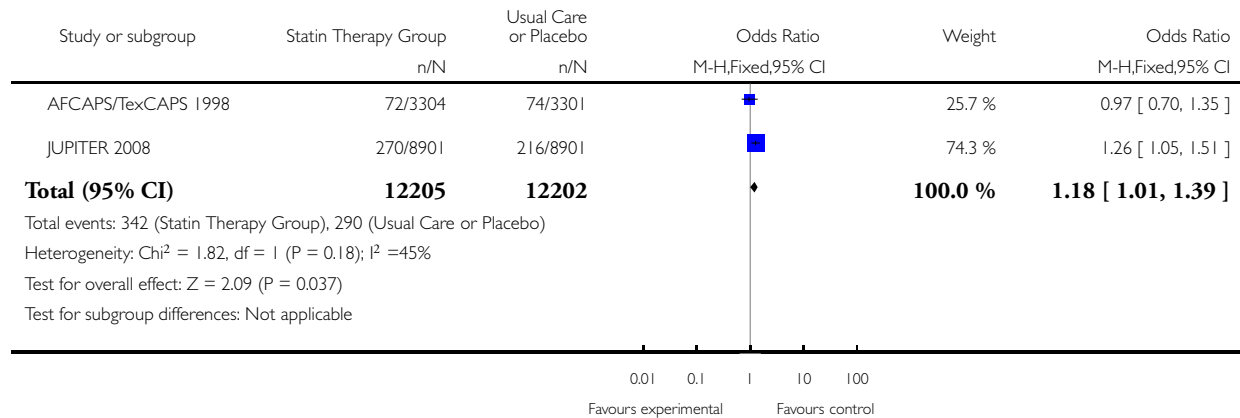


Analysis 3.7. Comparison 3 Adverse Events, Outcome 7 Number of study participants who developed diabetes.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 7 Number of study participants who developed diabetes

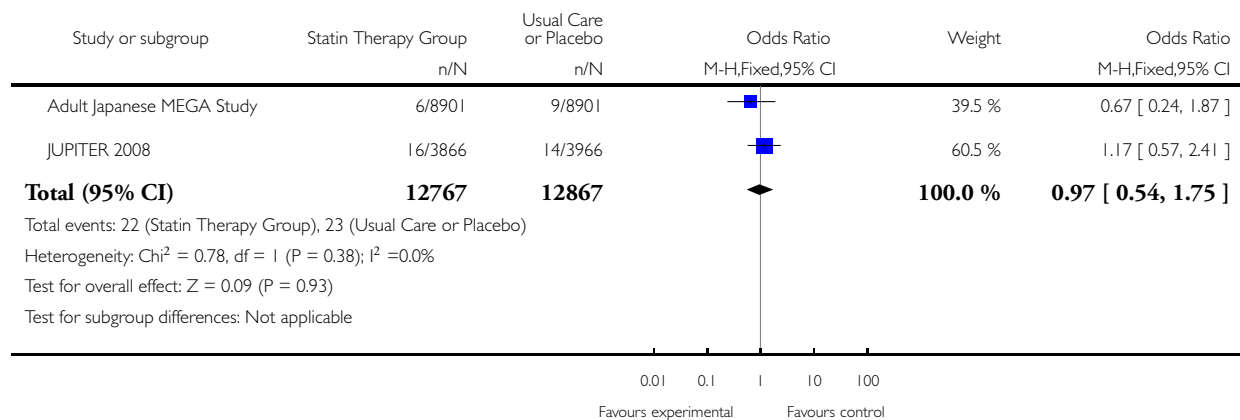


Analysis 3.8. Comparison 3 Adverse Events, Outcome 8 Number of study participants who developed haemorrhagic stroke.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 8 Number of study participants who developed haemorrhagic stroke

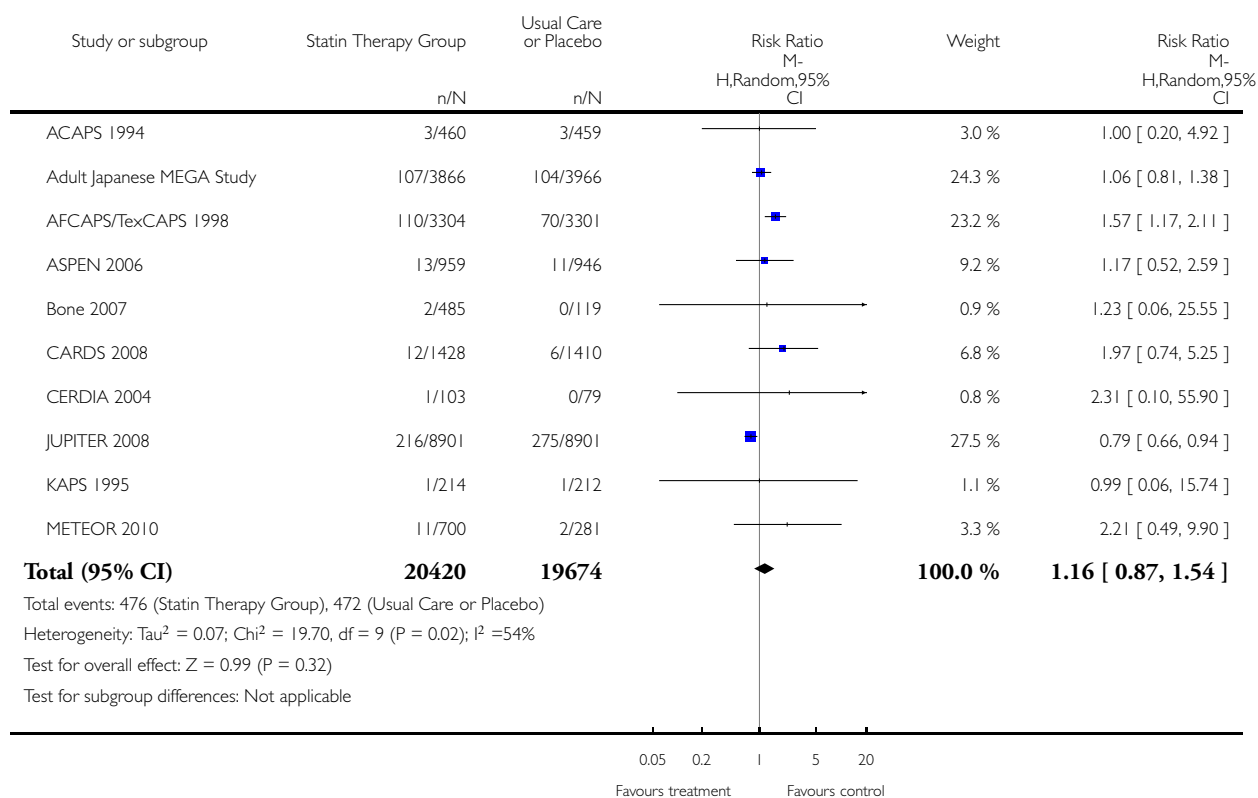


Analysis 3.9. Comparison 3 Adverse Events, Outcome 9 Number of study participants who had elevated liver enzymes.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 9 Number of study participants who had elevated liver enzymes

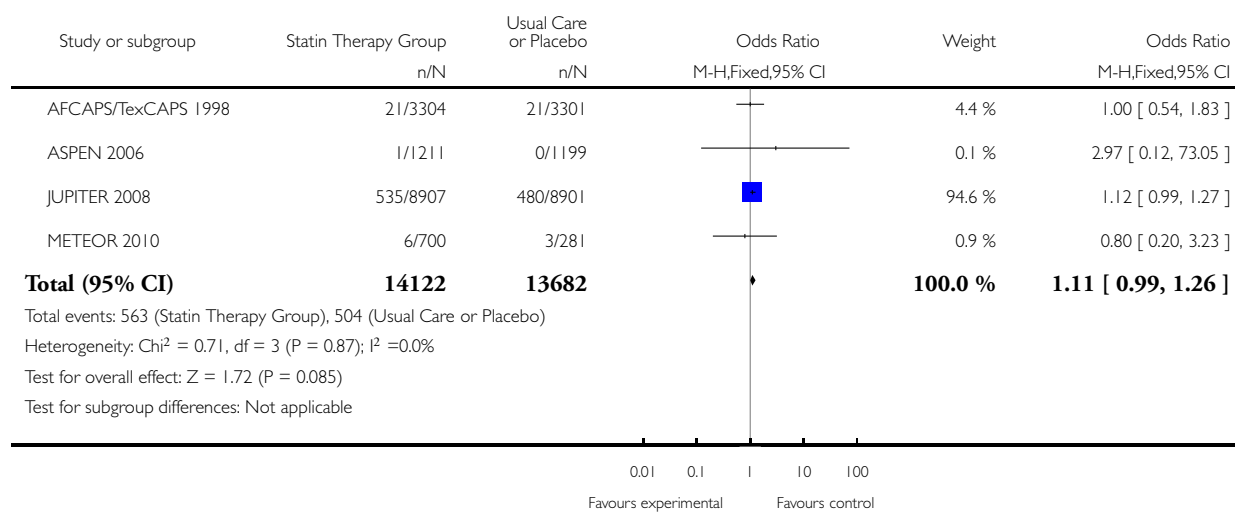


Analysis 3.10. Comparison 3 Adverse Events, Outcome 10 Number of study participants who developed renal disorder.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 10 Number of study participants who developed renal disorder

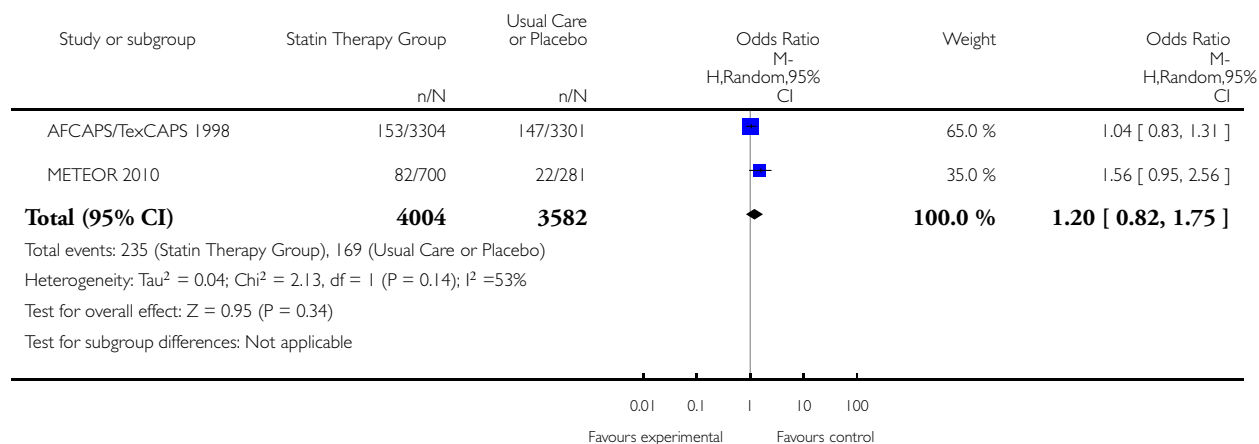


Analysis 3.11. Comparison 3 Adverse Events, Outcome 11 Number of study participants who developed arthritis.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 3 Adverse Events

Outcome: 11 Number of study participants who developed arthritis

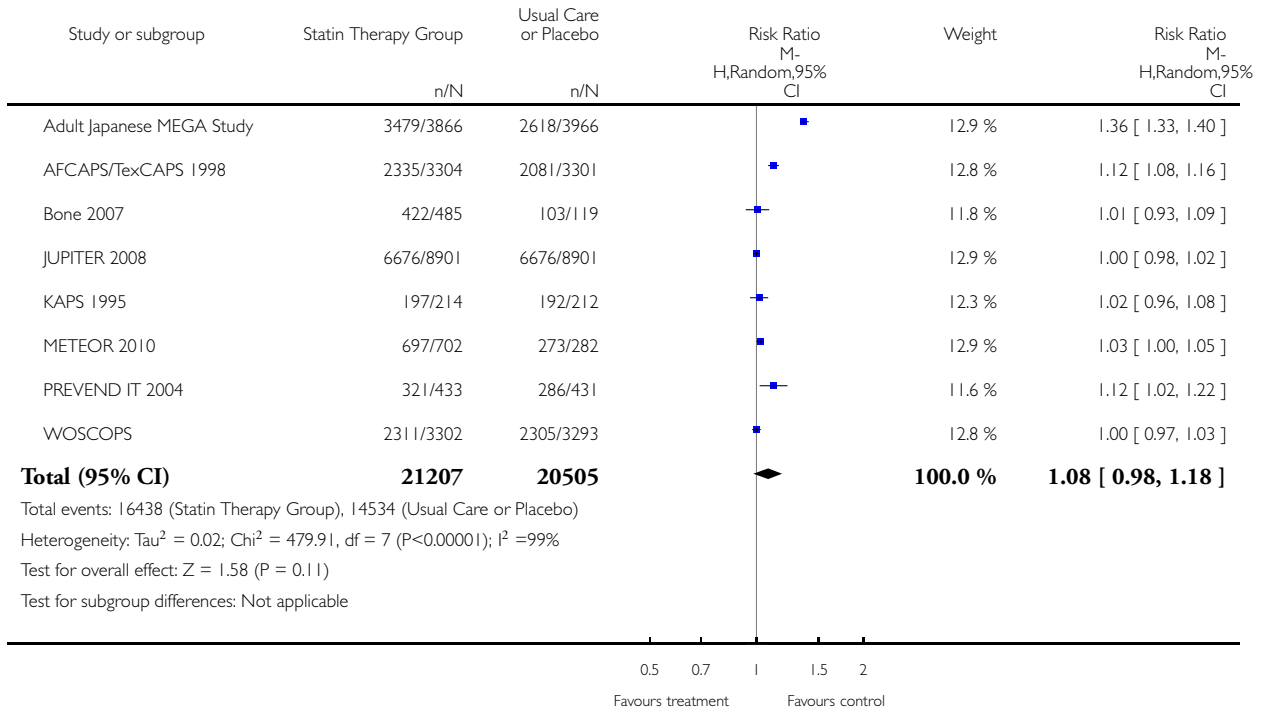


Analysis 4.1. Comparison 4 Treatment Compliance, Outcome 1 Treatment Compliance.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 4 Treatment Compliance

Outcome: 1 Treatment Compliance

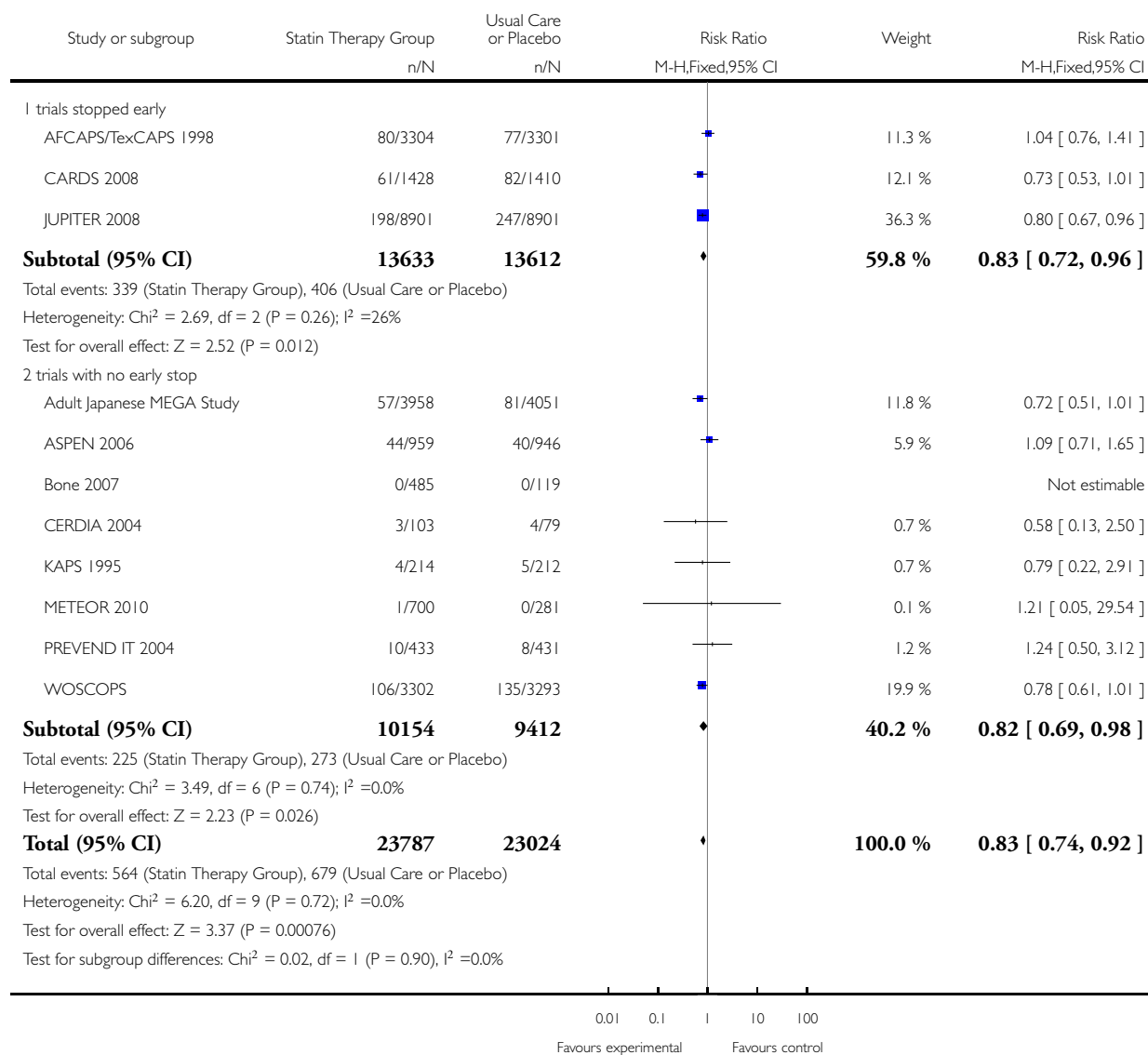


Analysis 5.1. Comparison 5 Sensitivity Analysis, Outcome 1 Early stopping of trials and total mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 1 Early stopping of trials and total mortality

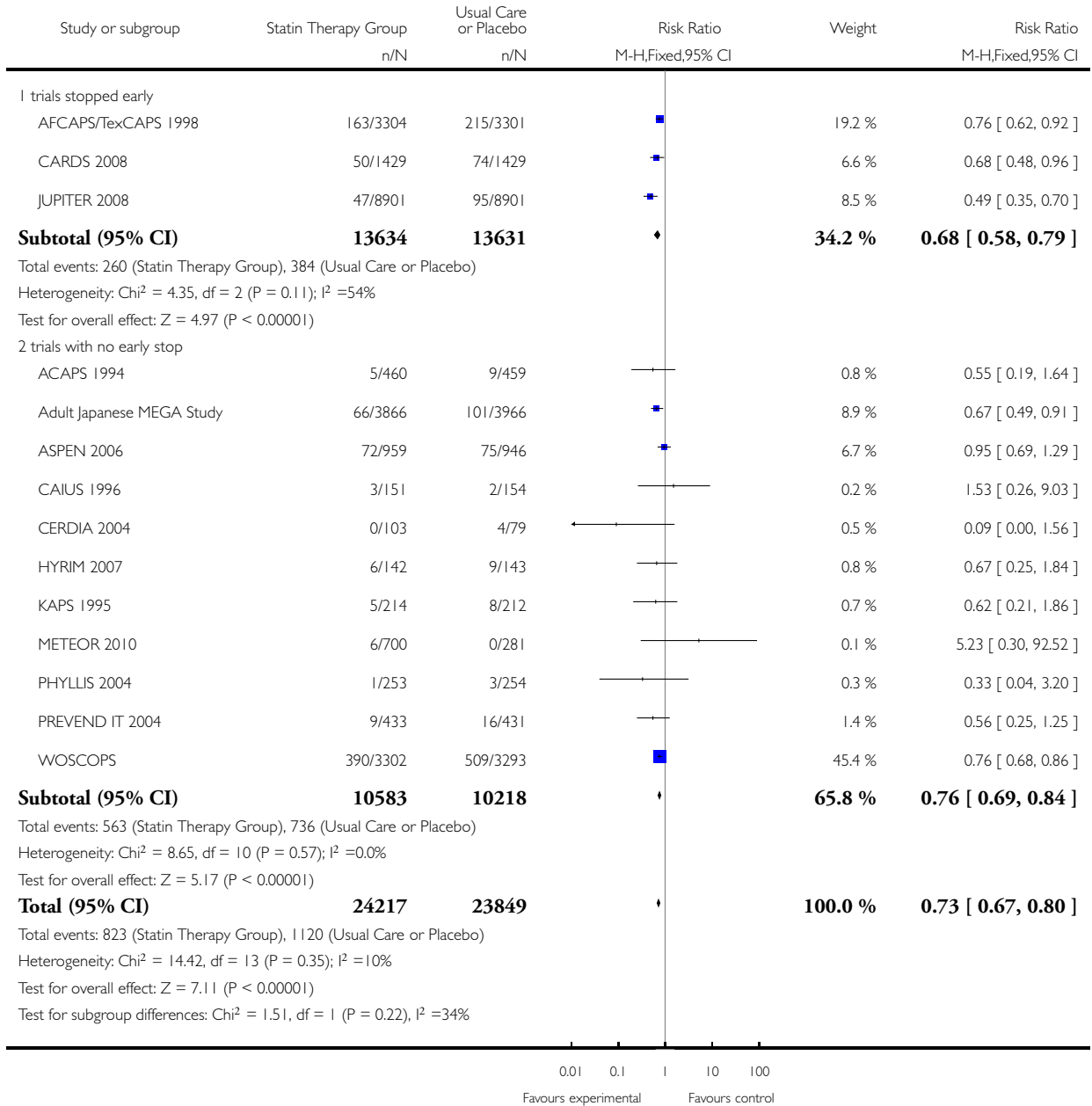


Analysis 5.2. Comparison 5 Sensitivity Analysis, Outcome 2 Early stopping of trials and total CHD events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 2 Early stopping of trials and total CHD events

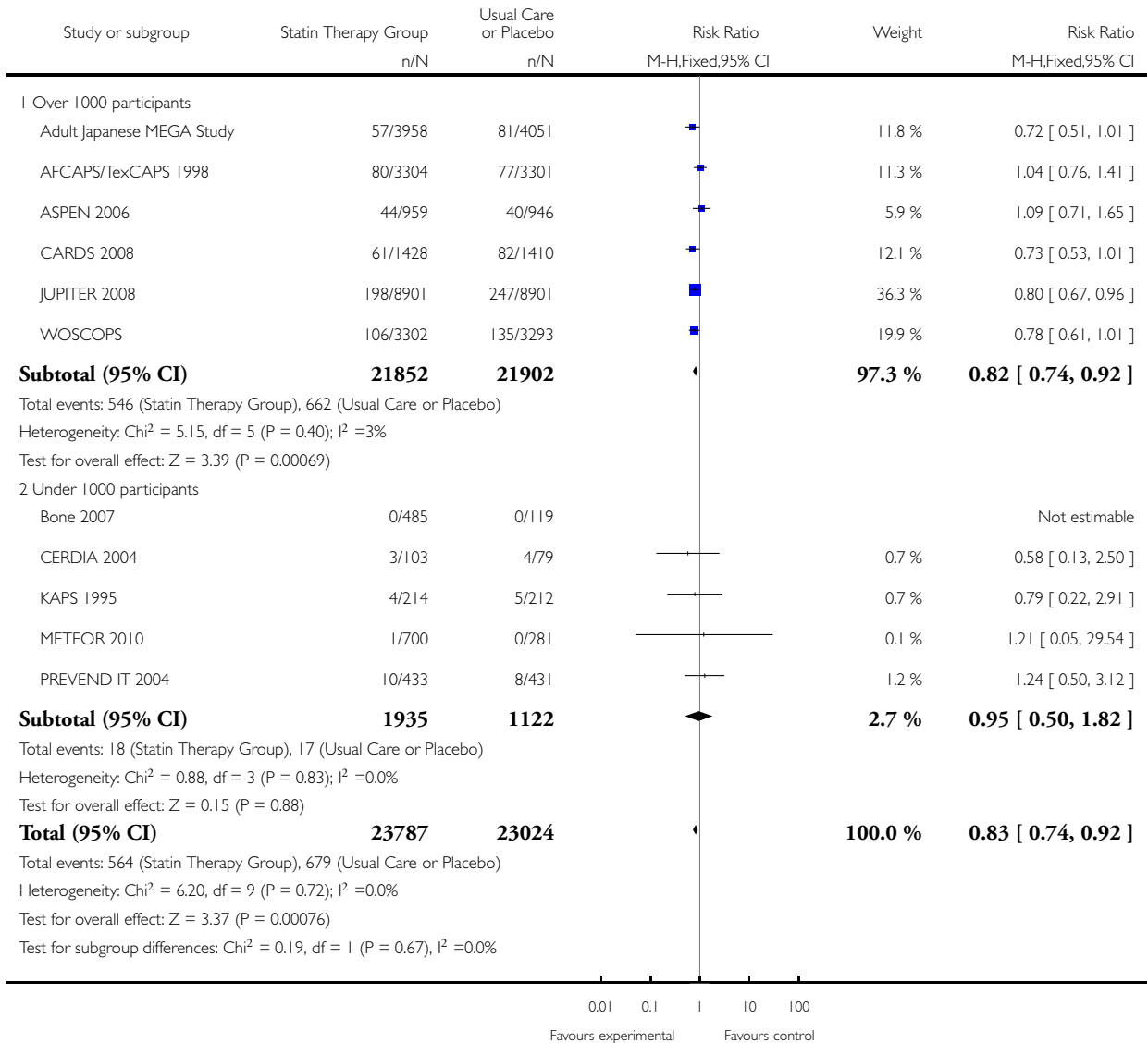


Analysis 5.3. Comparison 5 Sensitivity Analysis, Outcome 3 Study Size for total Mortality.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 3 Study Size for total Mortality

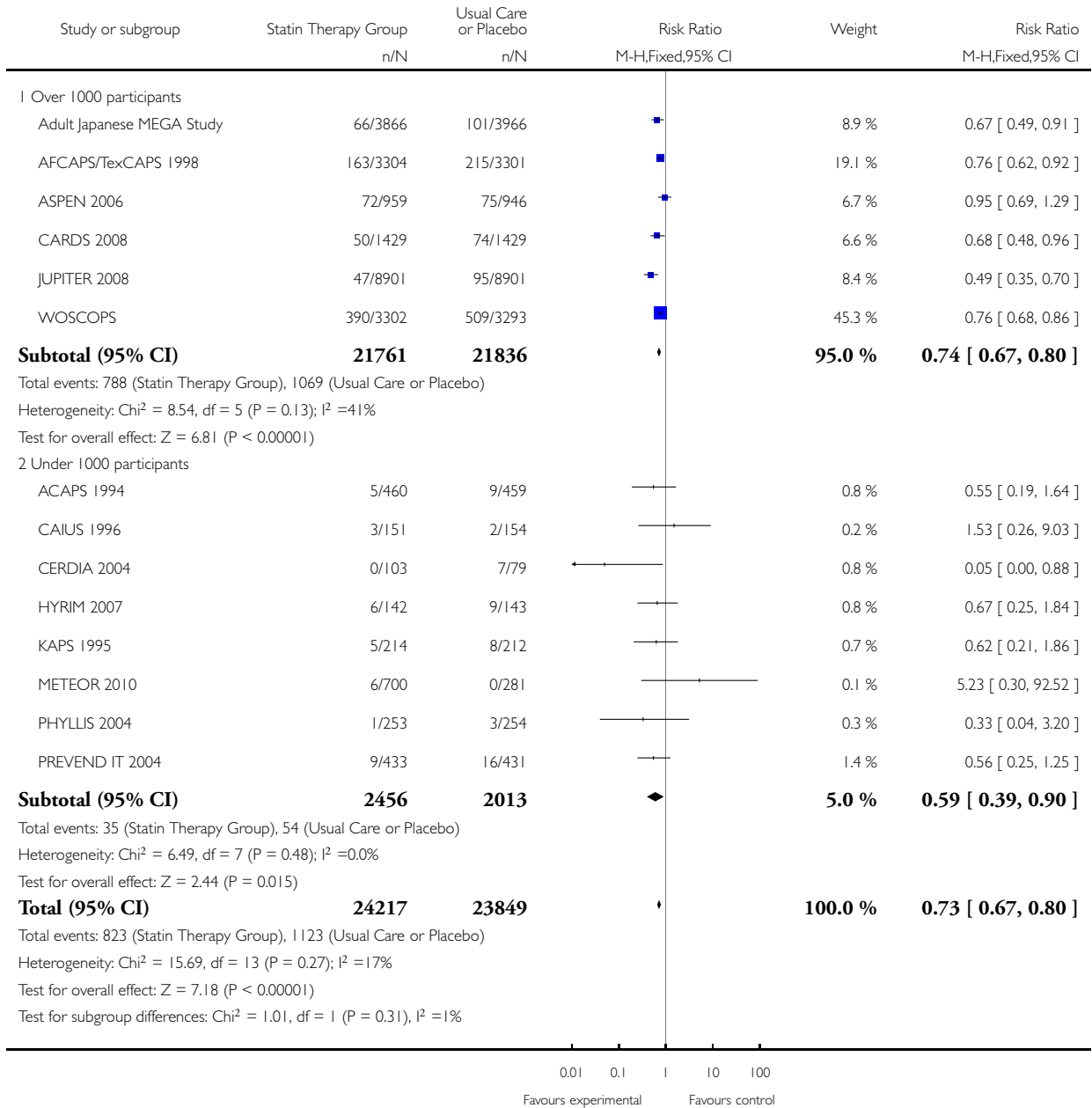


Analysis 5.4. Comparison 5 Sensitivity Analysis, Outcome 4 Study Size for total CHD events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 5 Sensitivity Analysis

Outcome: 4 Study Size for total CHD events



APPENDICES

Appendix I. Search Strategies 2007

CENTRAL on The Cochrane Library

- #1 MeSH 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)
- #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.
 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 altacor.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.
 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

Appendix 2. 2 Search Strategies 2012

CENTRAL

#1 MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees
 #2 hydroxymethylglutaryl*
 #3 HMG-CoA*
 #4 statin or statins
 #5 atorvastatin
 #6 cerivastatin
 #7 fluvastatin

#8 lovastatin
 #9 pravastatin
 #10 simvastatin
 #11 lipitor
 #12 baycol
 #13 lescol
 #14 mevacor
 #15 altocor
 #16 pravachol
 #17 lipostat
 #18 zocor
 #19 mevinolin
 #20 compactin
 #21 fluindostatin
 #22 rosuvastatin
 #23 dalvastatin
 #24 cranoc
 #25 canef
 #26 locol
 #27 lochol
 #28 leucol
 #29 lescol
 #30 monacolin
 #31 medostatin
 #32 mevinacor
 #33 livalo
 #34 pitava
 #35 pitavastatin
 #36 pravasin
 #37 mevalotin
 #38 gerosim
 #39 lipex
 #40 zenas
 #41 crestor
 #42 meglutol
 #43 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
 #44 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
 #45 (#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42)
 #46 (#43 OR #44 OR #45)

MEDLINE

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. hydroxymethylglutaryl*.tw.
3. HMG-CoA*.tw.
4. (statin or statins).tw.
5. atorvastatin.tw.
6. cerivastatin.tw.
7. fluvastatin.tw.
8. lovastatin.tw.
9. pravastatin.tw.
10. simvastatin.tw.
11. lipitor.tw.
12. baycol.tw.
13. lescol.tw.

14. mevacor.tw.
15. altocor.tw.
16. pravachol.tw.
17. lipostat.tw.
18. zocor.tw.
19. mevinolin.tw.
20. compactin.tw.
21. fluindostatin.tw.
22. rosuvastatin.tw.
23. dalvastatin.tw.
24. cranoc.tw.
25. canef.tw.
26. locol.tw.
27. lochol.tw.
28. leucol.tw.
29. lescol.tw.
30. monacolin.tw.
31. medostatin.tw.
32. mevinacor.tw.
33. livalo.tw.
34. pitava.tw.
35. pitavastatin.tw.
36. pravasin.tw.
37. mevalotin.tw.
38. gerosim.tw.
39. lipex.tw.
40. zenas.tw.
41. crestor.tw.
42. meglutol.tw.
43. or/1-42
44. exp Hyperlipidemias/
45. exp Cholesterol/
46. exp Cardiovascular Diseases/
47. cardio*.tw.
48. cardia*.tw.
49. heart*.tw.
50. coronary*.tw.
51. angina*.tw.
52. hyperlipid*.tw.
53. hypercholesterol*.tw.
54. cholesterol*.tw.
55. hypercholester?emia*.tw.
56. hyperlip?emia*.tw.
57. triglycerid*.tw.
58. hypertriglycerid?emia*.tw.
59. hyperlipoprotein?emia*.tw.
60. LDL.tw.
61. HDL.tw.
62. or/44-61
63. 43 and 62
64. randomized controlled trial.pt.
65. controlled clinical trial.pt.
66. randomized.ab.

- 67. placebo.ab.
- 68. clinical trials as topic.sh.
- 69. randomly.ab.
- 70. trial.ti.
- 71. 64 or 65 or 66 or 67 or 68 or 69 or 70
- 72. exp animals/ not humans.sh.
- 73. 71 not 72
- 74. 63 and 73
- 75. (2007031* or 2007032* or 2007033* or 200704* or 200705* or 200706* or 200707* or 200708* or 200709* or 20011* or 2008* or 2009* or 2010* or 2011*).ed.
- 76. 74 and 75

EMBASE

- 1. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
- 2. hydroxymethylglutaryl*.tw.
- 3. HMG-CoA*.tw.
- 4. (statin or statins).tw.
- 5. atorvastatin.tw.
- 6. cerivastatin.tw.
- 7. fluvastatin.tw.
- 8. lovastatin.tw.
- 9. pravastatin.tw.
- 10. simvastatin.tw.
- 11. lipitor.tw.
- 12. baycol.tw.
- 13. lescol.tw.
- 14. mevacor.tw.
- 15. altocor.tw.
- 16. pravachol.tw.
- 17. lipostat.tw.
- 18. zocor.tw.
- 19. mevinolin.tw.
- 20. compactin.tw.
- 21. fluindostatin.tw.
- 22. rosuvastatin.tw.
- 23. dalvastatin.tw.
- 24. cranoc.tw.
- 25. canef.tw.
- 26. locol.tw.
- 27. lochol.tw.
- 28. leucol.tw.
- 29. lescol.tw.
- 30. monacolin.tw.
- 31. medostatin.tw.
- 32. mevinacor.tw.
- 33. livalo.tw.
- 34. pitava.tw.
- 35. pitavastatin.tw.
- 36. pravasin.tw.
- 37. mevalotin.tw.
- 38. gerosim.tw.
- 39. lipex.tw.
- 40. zenas.tw.
- 41. crestor.tw.

42. meglutol.tw.
43. or/1-42
44. exp cardiovascular disease/
45. cardio*.tw.
46. cardia*.tw.
47. heart*.tw.
48. coronary*.tw.
49. angina*.tw.
50. hyperlipidemia/
51. exp cholesterol/
52. exp lipid blood level/
53. hyperlipid*.tw.
54. hypercholesterol*.tw.
55. cholesterol*.tw.
56. hypercholester?emia*.tw.
57. hyperlip?emia*.tw.
58. triglycerid*.tw.
59. hypertriglycerid?emia*.tw.
60. hyperlipoprotein?emia*.tw.
61. LDL.tw.
62. HDL.tw.
63. or/44-62
64. 43 and 63
65. ((2007* or 2008* or 2009* or 2010* or 2010* or 2011*) not (“200701” or “200702” or “200703” or “200704” or “200705” or “200706” or “200707” or “200708” or “200709” or “200710”)).em.
66. (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
67. retracted article/
68. 66 or 67
69. (animal\$ not human\$).sh,hw.
70. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
71. (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
72. 69 or 70 or 71
73. 68 not 72
74. 64 and 65 and 73
75. limit 74 to embase

FEEDBACK

Failure to cite CTT paper and dangerously misleading press release, 22 February 2011

Summary

Clinical Trials Services Unit and Epidemiological Studies Unit

The Discussion of your paper erroneously stated that the CTT collaborators had not published information about the proportional and absolute benefits of statin therapy among people with no prior history of vascular disease, although these were published in *The Lancet* in November 2010 (Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive LDL-lowering therapy: meta-analysis of individual data from 170,000 participants in 26 randomised trials of statin therapy. *Lancet* 2010; 376: 1670-81). It also stated that the CTT collaborators had been “unable to provide the relevant analysis for inclusion in our review”, but we are

not aware of having been asked by you (or anyone in your team) to provide such analyses, and wonder whether correspondence may have gone astray.

We are concerned that these mis-statements in the Cochrane Collaboration paper (and some over-statements in the related press release, such as the claim that “Given that low cholesterol has been **shown to increase** [our emphasis] the risk of death from other causes, statins may do more harm than good in some patients”) are dangerously misleading for the public -as well as not meeting the Cochrane Collaboration’s key principle of ‘keeping up to date’. Might it be possible for this Cochrane report to be corrected as a matter of urgency?

Professor Colin Baigent, Professor of Epidemiology, MRC Scientist, Hon. Consultant in Public Health
Professor Rory Collins, BHF Professor of Medicine and Epidemiology

Reply

The recent CTT Lancet November 2010 paper was not available to our team at the time the review was completed and submitted for publication to the Cochrane Database of Systematic Reviews. We agree that a data point in Figure 3 gives the proportional and absolute effects on major vascular events of a 1mmol/l reduction in LDL cholesterol in trial participants without prior cardiovascular disease. Our estimate of this effect and its precision is similar to the CTT estimate. I am surprised that CTT did not provide more information on other outcomes among participants taking statins for primary prevention. In particular, others have raised the issue of all-cause mortality in primary prevention trials (Ray et al, Arch Intern Med. 2010;170:1024-1031) and have expressed concerns about an increased risk of diabetes in those taking statins (Sattar et al, Lancet 2010;375:735-42). We will, of course, include reference to the CTT paper and will remove the text stating that CTT was “unable to provide the relevant analysis for inclusion in our review”. It should be feasible to make these changes in the next issue. Work is underway to conduct a comprehensive update of this review as soon as possible.

Following discussions with David Tovey and Rory Collins, the press release was withdrawn and a correction issued on 8 March 2011 from by David Tovey, Editor in Chief’s office on the homepage of the Cochrane Library (<http://www.thecochranelibrary.com/details/editorial/1029211/Correction-by-David-Tovey.html>). An email was sent to all recipients of that press release, and correction was attempted of any existing versions of the press release that were still in circulation.

Shah Ebrahim, lead author of Statins for the Primary Prevention of Cardiovascular Disease and Coordinating Editor of the Cochrane Heart Group

Contributors

Colin Baigent & Rory Collins, Shah Ebrahim

Further correspondence with CTT collaboration, 7 April 2011

Summary

22 February 2011

Taylor F et al. Statins for the primary prevention of cardiovascular disease.

Cochrane Database of Systematic Reviews 2011, Issue 1

The Discussion of your paper erroneously stated that the CTT collaborators had not published information about the proportional and absolute benefits of statin therapy among people with no prior history of vascular disease, although these were published in The Lancet in November 2010 (Cholesterol Treatment Trialists’ (CTT) Collaboration. Efficacy and safety of more intensive LDL-lowering therapy: meta-analysis of individual data from 170,000 participants in 26 randomised trials of statin therapy. Lancet 2010; 376: 1670-81). It also stated that the CTT collaborators had been “unable to provide the relevant analysis for inclusion in our review”, but we are not aware of having been asked by you (or anyone in your team) to provide such analyses, and wonder whether correspondence may have gone astray.

We are concerned that these mis-statements in the Cochrane Collaboration paper (and some over-statements in the related press release, such as the claim that “Given that low cholesterol has been **shown to increase** [our emphasis] the risk of death from other causes, statins may do more harm than good in some patients”) are dangerously misleading for the public -as well as not meeting the Cochrane Collaboration’s key principle of ‘keeping up to date’. Might it be possible for this Cochrane report to be corrected as a matter of urgency?

Colin Baigent & Rory Collins

Reply 2 March 2011

Re: Statins for the primary prevention of cardiovascular disease, Cochrane Database of Systematic Reviews 2011, Issue 1.

Thanks for your letter of 22 February 2011. The recent CTT Lancet November 2010 paper was not available to our team at the time the review was completed and submitted for publication to the Cochrane Database of Systematic Reviews. We agree that a data point in Figure 3 gives the proportional and absolute effects on major vascular events of a 1mmol/l reduction in LDL cholesterol in trial participants without prior cardiovascular disease. Our estimate of this effect and its precision is similar to the CTT estimate. I am surprised that CTT did not provide more information on other outcomes among participants taking statins for primary prevention. In particular, others have raised the issue of all-cause mortality in primary prevention trials (Ray et al, *Arch Intern Med.* 2010;170:1024-1031) and have expressed concerns about an increased risk of diabetes in those taking statins (Sattar et al, *Lancet* 2010;375:735-42). We will, of course, include reference to the CTT paper and will remove the text stating that CTT was "unable to provide the relevant analysis for inclusion in our review". It should be feasible to make these changes in the next issue.

The press release was referring to the association of low blood cholesterol (not cholesterol lowering by statins) with haemorrhagic stroke which has been shown by several observational cohorts, including a large Korean civil servants cohort (n=3900 haemorrhagic strokes), but these associations may be confounded. It would obviously be of great value to have a more reliable estimate of this effect by randomization to statins than that reported in the recent CTT paper (RR 1.12 (95% CI: 0.93, 1.35) per 1 mmol/L reduction in LDL cholesterol, webfigure 8) which might be achieved if more trials provided this outcome. More robust estimates would be particularly helpful for low and middle income countries where underlying rates of haemorrhagic stroke remain high and statins, as part of a "polypill" strategy, are being promoted for primary prevention.

We are already working on a full update of the review and have 7,000 citations to work through inclusion/exclusion criteria. In addition to the changes for the next issue, if you want I can arrange to have your letter and my response entered in the correspondence section linked to the review. This would enable your concerns to be immediately linked to the review and be readily available to readers of the review. Let me know your preference.

Shah Ebrahim

4 March 2011

Dear Shah

Thank you for your response. One quick point of clarification, the press release actually says "low cholesterol has been **shown to increase** [my emphasis] the risk of death from other causes" which is clearly quite different from what you have written in the second paragraph of your letter and is dangerously irresponsible. I wondered, therefore, if - before considering publication - you would like to make this error clear in your letter and ensure that the statement in the press release is formally retracted.

Rory Collins

04 March 2011

Dear Rory

I agree the wording is quite wrong. The press statement has not been published, nor is it available to readers of the review itself. I will add a sentence saying that a press release about the review contained a seriously misleading statement that "low cholesterol has been shown to increase the risk of death from other causes".

Shah Ebrahim

4 March 2011

Thank you for your proposal to modify your letter which is fine as far as it goes. The statement in this press release (which engendered wide publicity) is, however, so dangerously wrong that I think the Cochrane Collaboration is obliged to issue a public retraction. Please could you forward my correspondence to whoever is responsible for dealing with such serious misrepresentations within the Collaboration?

Rory Collins

4 March 2011

In the first instance, if we have published something that is misleading or incorrect in the press release I would suggest that we issue a correction in the release accompanying the next issue. I would like to explore with the writer of the release how this happened, as this is the first time that we have had such a complaint in relation to a press release, to the best of my knowledge. Having said that I am responsible for the sign off of press releases so that any error is entirely my responsibility.

I am making some enquiries as a matter of urgency and will let you all know when we have a proposed course of action.

David Tovey

4 March 2011

Shah Ebrahim has confirmed that the statement is wrong (see below) and, in public health terms, it is potentially a far more serious misrepresentation than that of the risks of MMR by Wakefield and The Lancet. As a consequence, I think it requires an urgent and specific response by the Cochrane Collaboration and should not just be “buried” in a routine press release.

Rory Collins

8 March 2011

This is to update you in relation to our current plans in relation to correction of the press release.

Firstly, we will contact via email in the next 48 hours, all individuals and agencies that received the original press release for Issue 1 and explain the need for a correction of the offending sentence. Secondly, we will publish a correction on The Cochrane Library homepage explaining the error. I anticipate that this will happen later today. Thirdly we will do our utmost to ensure that anywhere where the press release is still “live”, it is modified to a more satisfactory form of words.

The Cochrane Collaboration sets a high value on quality, scientific rigour and transparency. In this instance we are grateful to you for pointing out an error in the press release that had evaded our editorial system. Please be assured that we regarded this as a serious matter, and have sought to implement visible and appropriate measures to correct the error. We have also learned lessons from the episode that once implemented will reduce the chance of a similar event in the future.

David Tovey

10 March 2011

Thank you for taking some steps towards dealing with this problem as the errors of fact in both the press release, as well as those in the related paper (see our original letter to Shah Ebrahim and his reply: attached), have had a damaging effect on public health (as well as on the credibility of the Cochrane Collaboration). It is very much to your credit that you wish to take final responsibility (as editor) for these errors, but should not the authors also take some of the responsibility (rather than just passing the buck) since they presumably approved the press release which quotes them?

I have now had an opportunity to read your Correction on the Cochrane Library website and, though welcome, it seems to me that it is incomplete (given the errors in the original paper) and, indeed, is misleadingly half-hearted. For example, Shah Ebrahim accepts in his letter to us that, by contrast with what he had claimed in his paper, results for the highly statistical benefits in patients with no prior cardiovascular disease (risk ratio for major vascular events: 0.75; 95% CI 0.69 - 0.82) had been published nearly 3 months beforehand. Your Correction would have been an opportunity to put that straight, rather than to assert that such errors do “not impact in any way on the validity of the accompanying Cochrane Review”. Similarly, please could you explain why the claim in the press release that “low cholesterol has been shown to increase the risk of death from other causes, statins may do more harm than good” is, according to the assertion in your correction, “irrelevant to the underlying question being evaluated”? This does not seem to be correct.

I’m sorry not to have replied to your letter sooner, but I was waiting to see the Correction before doing so and was looking for it on the Cochrane Collaboration website, where it does not appear. As well as having it on the Cochrane Library website, would it not be appropriate to put this Correction (or, preferably, a more accurate one) on the Cochrane Collaboration website (and any other Cochrane websites), especially since the statin paper is one of its featured reviews?

I do hope that you will reconsider the partial (in more than one sense) attempt that you’ve made so far to redress the serious harm that has been caused to public health by the Cochrane Collaboration and its misinterpretation of the available evidence (which does not seem to be at all consistent with your key principles).

Rory Collins

10 March 2011

I suspect we have reached an impasse. I really don’t accept that the response was half-hearted. To repeat, we have placed a highly visible correction on the homepage of the product that was the subject of the press release, we have sent an email to all recipients of that press release, and we have sought to correct any existing versions of the press release that are still in circulation.

I, not the Co-ordinating Editor, sign off the press release, so this was my error alone. It was, as you pointed out, a seriously incorrect message - implying that the very act of reducing your serum cholesterol might cause early death - and could, if acted upon have caused public harm. For that reason I recognised the need to act decisively and swiftly to correct any wrong impression. I made the point in the correction that the press release mistake was based on a misunderstanding of the Cochrane Review, which had explicitly explained that any possible association was highly unlikely to be based on cause and effect. Therefore I believe it was correct to be clear that the press release was distinct from the review.

I recognise that you have also raised questions in relation to the content of the review. As Shah describes in his response, he has taken on board your comments, explained why the Lancet paper was not considered in the original published version, and has sought to amend the review appropriately at the earliest opportunity. For technical / publication reasons there will be an inevitable but short delay before the changes are published.

I am aware that you are unlikely to agree, but I am confident that our response to the questions you have raised in relation to the press release and the review has been appropriate, open and positive.

David Tovey

11 March 2011

I'm extremely grateful both for your careful response to my email and for what you've been able to do to rectify this problem. I did have a couple of questions in my previous email which I'd be grateful if you'd consider. First, might it be possible to put the Correction on the Cochrane Collaboration website as well, since that would be an obvious place where people alerted by the original press release would go? Second, why do you say in the Correction that the claim in the press release that "low cholesterol has been shown to increase the risk of death from other causes, statins may do more harm than good" is "irrelevant to the underlying question being evaluated" by this meta-analysis of whether statins do more harm than good? I had thought that this Correction would have provided an opportunity to indicate that errors in the original paper would also be corrected at the earliest possible opportunity.

Again, thanks for taking the issue so seriously and for going as far as you have towards repairing the damage caused.

Rory Collins

Reply

See above

Contributors

Colin Baigent & Rory Collins, Shah Ebrahim

22nd February 2012

Summary

Feedback: Dear respected authors and editors of the Cochrane Heart Group, First, in the abstract of the systematic review, statistically significant relative risk reductions were reported for all-cause mortality, non-fatal CVD events, and revascularisations. However, I had trouble applying this knowledge in practice because there was no mention of the absolute risk reduction or number needed to treat associated with statin use in this clinical setting. I thought these two values would be of clinical relevance since the review defined primary prevention as treating people without evidence of existing cardiovascular disease, who would be expected to have low baseline risks. Furthermore, despite the statistically significant relative risk reductions of key outcomes without an increase in adverse events found by this review, the authors advised caution before prescribing statins for primary prevention. This was a point of confusion for me, as I could not understand how the authors came to that conclusion. I think that because many people in the world have only access to the Cochrane abstracts and plain language summary, the rationale for the conclusions should be explicit to the reader. Lastly, on the abstract page this review was assessed as up-to-date on September 7, 2007, even though it was published on January 19, 2011. I was not sure if that was a mistake.

With Kind Regards,

Qiming Roger Wu

BSc, BSc(Pharm), RPh, MD Candidate

Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Dear Qiming Roger Wu,

Thank you for your feedback on this review of statins for primary prevention of cardiovascular disease. You would like to see absolute risk differences and numbers needed to treat. We have not provided these as they are often misleading in primary prevention. The absolute levels of CVD risk used will depend on a) what is included in 'CVD' (e.g. new angina cases, revascularisations), b) the population in which you practice (CVD incidence varies markedly between countries), c) age group and sex of the population considered. The

relative risk reduction figure is stable across outcomes, populations, age and sex groups. The NNT is not and presenting several NNTs is confusing for the reader.

You are concerned about why we recommend caution in using statins for primary prevention despite the statistically significant relative risk reduction. This is because the quality of the trials is variable (early stopping, selective reporting of outcomes), many do not report any adverse events (which is unlikely to be true), and guidelines in UK, USA and Europe do not recommend their use at levels below 20% 10-year risk of CVD. This is discussed in detail in the main text but not in the abstract for reasons of space. In the abstract we say: 'Other potential adverse events were not reported and some trials included people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost-effective and improve patient quality of life.' This gives some, but not all, of the rationale for use with caution. You question whether the review is as out of date as it appears. I am afraid it is. This is because doing a Cochrane review on statins requires searching for relevant papers - in this case we had to sift through thousands of abstracts of papers, retrieve hundreds of full papers, assess them in duplicate to reach our final 14 trials for consideration. This takes time and in this case was made worse as the key authors were relocated to work in India on another project that took priority over this review. We have conducted an update and hope that this will be published before the end of 2012.

Thank you for your interest in our work.

Best wishes, Shah Ebrahim

Contributors

Qiming Yu, Shah Ebrahim

Response to Taylor et al (2013) Statins for primary prevention of cardiovascular disease

Summary

Dear Colleagues,

I am writing to express concerns about the Cochrane Review update of statins for primary prevention (Taylor et al 2013.) I have three principle concerns which involve Taylor et al's treatment of 1) potential commercial bias, 2) data transparency, and 3) patient safety.

Recent research indicates that commercial bias may be an important factor in evaluating the validity of published trial data and may be more important than a checklist of technical factors in determining bias. Bero, Lexchin, Lundh and other colleagues, for example, have pointed out a variety of issues in this regard (eg Bero et al 2007; Roseman et al 2012; Lundh et al 2012). Most recently, describing the research of Lundh et al's (2012) Cochrane Review on industry sponsorship and research outcomes, Bero (2013; JAMA Intern Med) has stated that standard assessment tools do not adequately grapple with risk of bias. She noted that Lundh et al (2012) reviewed nine studies with seemingly low risk of bias but the relationship between sponsorship and outcomes was in fact stronger. The Cochrane authors, citing Als-Nielsen (2003) note the possibility of commercial bias briefly but fail to explain why they do not consider it more fully in their analysis.

Will the authors clarify why they did not fully address commercial sponsorship as a risk of bias?

Taylor et al (2013) rely heavily on industry-sponsored trials and the meta-analysis by the CTT indicating that the CTT's commercial sponsorship is an analysis rests in their use of patient-level data. However, it is known that many scholars have asked the CTT for data without success (inter alia Criqui and Golomb 2004, Walsh and Pignone 2004, Petretta 2008.) As I understand the Review by Taylor and colleagues they seem not to have reviewed that data but are relying on the CTT's interpretations. Currently many scholars are asking for transparency and the release of primary source data like Clinical Study Reports and patient-level data (eg Doshi and Jefferson) so that the larger scientific community can be more fully informed. This broader perspective is important in understanding both benefit and harm through a lens other than that provided by industry.

Will the authors clarify why they did not ask for full transparency but seemingly relied on CTT analysis?

In terms of issues related to harm, the Review is both troubling and confusing. It is known that harms are under-reported in commercial trials. The Cochrane authors state that 12 trials provided data on Adverse Events, indicating that one third did not provide data on

AEs. They previously stated (page 3) that the trial authors were contacted to obtain further details. It is, thus, not clear if the AE data was withheld from the Cochrane reviewers or were not collected in the original trials. The authors state (page 14) that reporting of adverse events in the statin trials is relatively poor, since there is a failure to provide important details of type and severity of AEs. But they then state with (no citations) that it “seems unlikely that major life-threatening hazards associated with statin use exist.” And they go on to state that potential non-fatal but serious adverse events have not been assessed in statin trials. They briefly touch on the recent work by Hipsley-Cox (20120) but seem to discount the value of database analysis for detecting statin harm. It is, thus, not clear why Taylor and colleagues have chosen to deem statins safe for primary prevention for men and women on the basis of clinical trial data with serious limitations in safety information. Nor is it clear why they did not consider information about harm from a wider variety of sources including advisories from countries like New Zealand, UK and the USA. Many sources indicate that clinical trials are not geared towards real-world experiences of harm. For example, Fernandez and colleagues at the Cleveland Clinic (2011) state that statin myopathy is a common experience that is not reflected in clinical trials and that muscle symptoms occurred in up to 20% of patients on statins. They point out that real-world conditions should be considered, and note the relatively low level of myalgia (1%-5%) described in clinical trials. Other institutions have, like the Mayo Clinic, have created Statin Intolerance Clinics acknowledging people’s every day experiences with statin harms. Oskarsson (2011; Neurology) states that there is particular concern about necrotizing statin myopathy wherein recovery does not occur with cessation of statin-exposure. (See also research by rheumatologists like Mammen and colleagues on treatments for statin-associated autoimmune necrotizing myopathies.)

Pharmacovigilance can play an important role in detecting signals of harm, which the Cochrane authors do not fully consider. Sakaeda et al (2011) analyzed data on muscular and renal events in FDA data base and found evidence of signals of harm warranting clinical trial research. There is also an important social context in adverse event reporting. Research indicates adverse event reporting to be low, possibly because of failure to recognize statin associated symptoms (Dirks and Jones, 2006) or physician reluctance to report (Golomb et al., 2007.) Taylor and colleagues have also not dealt with the issue that statins are considered a category X drug in the USA and are associated with miscarriage and birth defects (see for example Edison and Muenke, 2004 and Prescrire 2005.) Taylor and coseem to suggest that women of child-bearing capacity (over age 35; page 15) would benefit from statins without considering this important harm. Taylor and colleagues indicate that in using CTT patient level data they have examined the “totality of evidence” for primary prevention statin use.

This does not seem possible. I am concerned that the voices of patients are not heard in this review. I do not see evidence of pro-active research strategies addressing patient safety. The importance of interrogating the quality of safety reporting in clinical trials is seen as valuable within the research community but it is raised in a confusing way in this review; both acknowledging problems and then discounting their relevance. Other sources of data are not adequately considered.

Will the authors explain what they mean by “the totality of evidence” and why they have not attempted to proactively secure safety data from trialists nor consider other forms of independent information about statin-related harms?

Harriet Rosenberg, York University, Health and Society Program (retired)

Reply

Thank you for your interest in our review. We respond to your questions and hope you find them helpful in understanding our approach, both its strengths and its limitations.

1. Will the authors clarify why they did not fully address commercial sponsorship as a risk of bias?

The potential bias associated with commercial sponsorship of trials is well-recognised. We collected and reported information on the funding source of all trials included in our review. We were unable to evaluate this form of potential bias through comparison of effect sizes between commercially funded trials and non-commercially funded trials, since every trial was commercially funded. We have addressed commercial sponsorship to the extent possible in this circumstance. We would be pleased to learn of alternative approaches in these circumstances.

2. Will the authors clarify why they did not ask for full transparency but seemingly relied on Cholesterol Treatment Trialists (CTT) analysis?

Our analysis did not rely on the CTT analyses. Our meta-analyses are based on published data from trials on statins. CTT is based on individual patient data and covers an overlapping set of statin trials in both primary and secondary prevention. We are aware that attempts to obtain individual patient data from CTT does not appear to be feasible, and we did not ask the CTT investigators for data

as we did not require their data to carry out our systematic review. It is important to recognise that in any systematic review using Cochrane methods a thorough search is made for all relevant trials, independent of source of funding. We then conducted our analysis using published data and made requests to the individual trial authors, where necessary, for data on specific outcomes. As the CTT had published highly relevant analyses since our 2011 publication, it was imperative for us to update our review in light of their findings. Our findings obtained from the published literature and findings from the CTT are remarkably similar, so we do not believe that there are any issues with the integrity of their analyses.

3. Will the authors explain what they mean by “the totality of evidence” and why they have not attempted to proactively secure safety data from trialists nor consider other forms of independent information about statin-related harms?

We considered the randomized evidence in this Cochrane review and on that basis believe we have the totality of this evidence. We have attempted to get additional information from trialists but did not set out to duplicate successful efforts that have others have made to get additional data. CTT have been particularly successful in this regard (as have others with respect to type 2 diabetes). Individual patient level data are needed to do this well and is a long term goal for our group. We have also considered other non-randomized data in our discussion.

We concluded that it “seems unlikely that major life-threatening hazards associated with statin use exist.” This is based on the all-cause mortality relative risk of 0.86 (95% CI 0.79 to 0.94). This means that, overall, any unintended effect of statins that was severe enough to cause death would be highly unlikely as we do not see any increased overall death rate on statins. We accept that trials generally do not report unintended effects of treatments well, and statin trials are no exception.

The analyses from the CTT have explored the possibility of hazards due to cancers and found no evidence of any increased risk of any cancer. We believe these data are reliable and are consistent with our own analyses from the trial reports. We also considered myalgia/rhabdomyolysis, type 2 diabetes, haemorrhagic stroke, liver dysfunction, renal dysfunction and arthritis.

We also examined adherence with treatment rates and found 77% participants and 70% in the placebo group complied with treatment; RR 1.08 (0.98 to 1.18), indicating that while 23-30% of patients stopped treatment, this was more common in those taking placebo than in those taking statins.

We have not made any specific reference to use of statins in women of child-bearing age, in whom it would be most unlikely for statins to be indicated. We do report that women gain similar benefit to men, which was not clear in previous reviews.

With regard to other potentially serious, but non-fatal unintended effects of statins, we do not discount Hipsley-Cox’s report (or Smeeth’s report) as large scale observational data are often the only way of determining possible unexpected harms. However, they are prone to confounding and do not provide the robust evidence that randomized trials do.

There are many observational reports of harms associated with statins, and this literature frequently reports contradictory findings. We are currently conducting a separate systematic review of these studies and are also conducting a further large scale primary care database analysis. These studies are complex to perform, have taken separate funding to conduct, yet should be ready for submission for publication later this year.

Contributors

Shah Ebrahim, George Davey Smith, Tess Moore, Fiona Taylor and Mark Huffman

Query regarding outcomes and mortality figures, 10 December 2013

Summary

1. Why did you decide to use the 10 year follow-up (‘post-trial period’) and not the ‘trial period’ outcomes for the WOSCOPS study (Tables 1 and 2, NEJM 2007 357;15,1477-1486) for the quoted outcomes? This increases the weighting of WOSCOPS greatly and affects the event rate and subsequently ARR or NNT based on control rates.

2. Where did you source the PREVENT-IT total mortality figures of 10/433 in the statin group and 8/431 from? This is not clear to me from reading the source paper and other meta-analyses list the figures as 13/433 and 12/431 respectively (Tonelli M et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ 2011. DOI:10.1503/cmaj.101280 and Ray K et al Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65 229 Participants. Arch Intern Med. 2010;170(12):1024-1031).

Dr Rupert Major, University of Leicester.

Reply

1. If there are longer follow ups available it does make some sense to use them to increase the overall events, particularly if they are sparse which is the case in trials of primary prevention. However, it is generally better to carry out two analyses: trial end outcomes and longest outcomes to explore how publication of longer follow ups may be biasing the overall effect size. There is a tendency for trialists who have found continued benefits to publish such data but not to publish if these findings if they are null. We will carry out this analysis in the next update of this review.

NNTs are highly susceptible to the underlying rates used to estimate them and, in my opinion are potentially quite spurious when derived from trial control groups (which tend to be healthier than the populations in which drugs are used, even in primary prevention). Sensitivity analyses are always worth doing using trial control group rates, general population rates (often available from large GP databases), and separated by gender and age groups.

2. With regard to the data abstracted for PREVENT-IT, I am not able to confirm the source of the data used as I will not be in London where the data abstraction sheets are stored - and won't be until end of February. It is quite possible that these are errors given your cross-checking with the original paper and other meta-analyses. So thank you for drawing my attention to this and it will be checked, and if in error, corrected in the next update.

Contributors

Shah Ebrahim and Rupert Major.

Calculation of NNT, 17 January 2017

Summary

At our department we teach EBM to doctors in training for general practice. One of our students have studied statins in primary prevention and used your review thoroughly.

In the calculations of NNT she (ABH) had difficulties following your calculations and two senior researchers (AM+OO) could not help her out.

In relation to total mortality you state:

"All-cause mortality. Thirteen trials with 48,060 participants recruited reported on total mortality. During observation, 1077/24,408 (4.4%) died in the statin group compared with 1223/23,652 (5.1%) in the placebo group; number needed to treat for five years: 96 (95% confidence interval (CI) 64 to 244)."

However, we calculate ARR: $5.1\% - 4.4\% = 0.7\%$, and if we use the traditional formula $NNT = 1 / ARR$, we get $NNT = 143$, i.e. larger than your $NNT = 96$.

Similarly, in relation to fatal and non-fatal CHD events you state:

"Fourteen trials with 48,049 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-effect model: 820/24,217 (3.4%) in the statin group versus 1114/23,832 (4.6%) in the placebo group. Overall NNT for five years: 56 (95% CI 46 to 75);"

But we get ARR = $4.6\% - 3.4\% = 1.2\%$, and thus $NNT = 83$, i.e. again larger than your $NNT = 56$.

We cannot see in your methods section that you have used any other formula than the usual.

Could you please explain how your NNTs have been calculated?

Best regards,

Anne Boe-Hansen Dall MD, Anne Møller, MD, PhD, Ole Olsen, M.Sc.

Reply

The discussions of numbers needed to treat (NNT) for total mortality and for fatal and non-fatal CHD events have been revised to reflect both unadjusted NNTs (calculated directly from the summary data for the trial outcomes) and NNTs adjusted to account for total person-years of follow-up across all studies in each outcome (in order to account for the differences in study duration across trials)

(1)

1) Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses--sometimes informative, usually misleading. *BMJ*. 1999 Jun 5;318(7197):1548-51.

Contributors

Mark Huffman, review author
William Cayley, Cochrane Heart feedback editor

WHAT'S NEW

Last assessed as up-to-date: 1 January 2012.

Date	Event	Description
21 April 2017	Amended	Text edited for all-cause mortality and fatal and non-fatal CHD events in response to feedback
21 April 2017	Feedback has been incorporated	Comment on calculation of NNT and reply added.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2011

Date	Event	Description
18 August 2016	Amended	Minor corrections on decimal points for outcomes fatal and non-fatal CVD events and fatal and non-fatal stroke events)
2 October 2014	Amended	Contact person changed from Fiona Taylor to Mark Huffman. Acknowledgements amended, adding thanks to translators.
20 January 2014	Feedback has been incorporated	Query regarding the timing of outcomes and the mortality figures of the PREVENT-IT trial
11 April 2013	Feedback has been incorporated	New feedback was added
4 December 2012	New citation required and conclusions have changed	This update includes 4 new studies and updated data from 3 studies and our conclusions have changed

(Continued)

18 June 2012	New search has been performed	This review has been updated incorporating findings from the Cholesterol Treatment Trialists Collaboration individual patient data meta-analyses that extend the findings on benefits of statins to people at lower risk of major cardiovascular events than previously established. Conclusions have been changed
10 April 2012	New citation required and conclusions have changed	New search to January 2012 found four new trials and published follow-up data on three existing trials. Results and conclusion have changed in light of the new evidence
10 April 2012	Feedback has been incorporated	Feed back incorporated.
4 July 2011	Amended	Rectified minor error in reporting of all-cause mortality data in main text
7 April 2011	Feedback has been incorporated	Correspondence with CTT collaboration added
7 April 2011	Amended	Converted to new review format
8 March 2011	Feedback has been incorporated	Removed text indicating CTT collaboration had not provided relevant data. Included citation to recent CTT collaboration paper which gives additional confirmation of benefits of statins in primary prevention. Added in response to CTT collaboration correspondence (see Feedback)

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.

Mark Huffman: Helped screen abstracts for the update, contributed to the analysis and interpretation of data for the update.

Ana Macedo: Abstracted data for the update, helped assess adverse events and wrote to authors.

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 in addition to screening of abstracts for the update

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

DECLARATIONS OF INTEREST

None known.

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- Department of Social Medicine, University of Bristol, UK.

External sources

- Department of Health Funding for the Cochrane Heart Group, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiovascular Diseases [blood; mortality; *prevention & control]; Cause of Death; Cholesterol, HDL [blood]; Cholesterol, LDL [blood]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*adverse effects; therapeutic use]; Myocardial Revascularization [methods]; Primary Prevention; Randomized Controlled Trials as Topic; Stroke [prevention & control]

MeSH check words

Adult; Humans