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Legacy effects of statins on cardiovascular and all-cause mortality - A meta-analysis

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Legacy effects of statins on cardiovascular and all-cause mortality

- A meta-analysis

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Abstract

Objectives: To assess evidence for "legacy" (post-trial) effects on cardiovascular (CVD) and all-cause mortality among adult participants of placebo controlled randomised trials (RCTs) of statins.

Design: Meta-analysis of aggregate data

Setting/Participants: placebo controlled statins RCTS for primary and secondary CVD prevention

Methods: Data Sources: PubMed, Embase from inception and forward citations of Cholesterol Treatment Trialists' Collaborators RCTs to 16th June 2016.

Study Selection: two independent reviewers identified all statin RCT follow-up reports including ≥1000 participants, and cardiovascular and all-cause mortality (0.5% of initially identified studies).

Data Extraction and Synthesis: Independent data extraction was done by two reviewers according to PRISMA guidelines.

Main Outcomes: post-trial CVD and all-cause mortality.

Results: We included 8 trials, with mean post-trial follow-up ranging from 1.6-15.1 years, and including 13,781 post-trial deaths (6,685 CVD). Direct effects within-trials were greater than legacy effects post-trials. The pooled data from all eight studies showed no evidence overall of legacy effects on CVD mortality, but some evidence of legacy effects on all-cause mortality (p=0.01). Exploratory subgroup analysis found possible differences in legacy effect for primary prevention trials compared to secondary prevention trials for both CVD mortality (p=0.15) and all-cause mortality (p=0.02). Pooled post-trial hazard ratios for the three primary prevention studies demonstrated possible post-trial legacy effects on CVD mortality (HR=0.87; 95% CI 0.79-0.95) and on all-cause mortality (HR=0.90; 95% CI 0.85-0.96).

Conclusions: Possible post-trial statin legacy effects on all-cause mortality appear to be driven by the primary prevention studies. Although these relative benefits were smaller than those observed within-trial, the absolute benefits may be similar for the two time periods. Analysis of individual patient data from follow-up studies after placebo controlled statin RCTs in lower risk populations may provide more definitive evidence on whether early treatment of subclinical atherosclerosis is likely to be beneficial.

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Keywords

Hydroxymethylglutaryl-CoA Reductase Inhibitors
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Strengths and limitations of this study

- Our sensitive search strategy means this study is likely to have included all follow-up reports of the major placebo controlled statin trials, including recent follow-up reports for two of the studies (WOSCOPS and LIPID).
- We focus analysis on the post-trial period which is best for detection of legacy effects,
- However, post-trial data are no longer a randomised comparison, and legacy effects may be larger than we estimated.
- The main limitation is that our findings are based on aggregate data, and we did not have information on whether or not an individual was treated with statins during the post-trial period, and for how long, as well as their cardiovascular risk factor levels and other confounders.

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Competing Interest Statement: All authors have no competing interests to declare.

Introduction

'Legacy effects' are treatment effects that persist or emerge at some time after trial treatment ends. The existence, or not, of such legacy effects have important clinical implications, including the potential value of early starting of treatment and the risks of treatment cessation. Although technically even short term or transient improvement or worsening of symptoms and signs may be classified as a legacy effect, most people appear to use the term to indicate sustained clinical benefit or harm.(1-7)

Recently there has been considerable interest in the possible legacy effects of statins,(8, 9) sparked by reports on the long term outcomes for participants of large placebo controlled trials. In some of these reports,(4, 10) there is still a persistent survival advantage to participants who were randomised to statin during the trial, even though there was no or minimal difference in management of participants after the trial ended. Legacy effects could indicate that earlier treatment with statins slows atherosclerotic plaque build-up in arteries and so alters the natural disease progression during a person's lifetime. This is supported by noted differences in long term response to statins for primary prevention trials compared with secondary prevention.(11) To this end, aggressive lipid lowering therapy in much younger individuals with lower risk for cardiovascular disease has been suggested as a possible means of primary prevention. Some have argued for universal screening of cholesterol levels in young people and offering early statin treatment to those with raised levels,(12-14) whereas others have argued that statins be offered to all young people, regardless of cholesterol levels. (5, 15)

At least some of the survival benefit observed on long term follow-up is attributable to the direct treatment effects on cardiovascular disease outcomes observed during the within-trial period. For example, survival curves may be generated by simulating an intervention which only has effects during the trial period, and not after the trial (Figure 1A). A persistent

survival benefit is observed, but all of this is due to direct effects during the initial trial period. If hazard curves are constructed instead, then there is no persistent benefit observed (Figure 1B; details of the methods for the simulation are provided in the Appendix). Although survival curves like Figure 1A demonstrate that the direct effects of the intervention (observed during the trial period) are still apparent many years later, they do not provide evidence of indirect effects after the intervention has ceased. To demonstrate such indirect effects, or legacy effects, we need to focus on outcomes observed during the post-trial period. To this end, we aimed to identify and combine estimates of the effect of trial treatment group allocation on post-trial all-cause and CVD mortality from published reports on the long term follow-up after placebo controlled trials of statins.

Methods

Protocol and Registration

The review protocol was not registered.

Selection

We performed a systematic search and meta-analysis of all reports on follow-up after randomized, placebo-controlled studies of adults (age >18 years) of statins with ≥1000 participants. We excluded studies that did not report mortality data during post-trial follow-up. The primary outcomes were death due to all-causes and due to cardiovascular disease.

Search strategy

We identified placebo controlled RCTs of cholesterol lowering treatment from the Cholesterol Treatment Trialists' Collaboration (16) and ran forward citation searches in Scopus; search was limited to those citations which included one of the investigators from the RCT. We searched for additional reports in Medline and Embase with no earliest date

restriction, though to 16th June 2016 using the terms listed in Box 1, with no restrictions on year published, type of publication, or language. We checked references of included studies to identify further relevant papers and contacted trialists to identify updated or additional reports.

Box 1: Search strategy:

1 Follow-Up Studies/

4 random$.tw

7 placebo.tw

9 Hydroxymethylglutaryl-CoA Reductase Inhibitors/

10 cholesterol/

11 lipids/

10 (#1) AND (#2) AND (#3) AND (#9 OR #10 OR #11)

Validity assessment

We extracted data for both within-trial and post-trial periods on the following characteristics which may bias the estimated legacy effect: Mean follow-up (years), Difference in proportion taking statins.

Study selection and data abstraction

Two authors (AN and KB) checked the titles and abstracts of all citations identified through the database searches and forward citation search. Full text was obtained if either author judged the article potentially relevant. The same two authors then independently checked all the full text articles for eligibility, resolving disagreements through discussion.

Two authors independently extracted clinical data (AN and LZ) using standardized forms, deciding disagreements through discussion with a third author (KB). We extracted separate

data on all-cause mortality and CVD specific mortality for the within-trial and post-trial periods; the number of people at risk of each type of event at the start of the trial and at the start of the post-trial follow-up; the proportion of people taking statins within trial and post-trial; the duration of follow-up within trial and post-trial. We attempted to extract differences in mean total cholesterol, but these were missing for at least one of the periods in the majority of studies. Further data on the original trials was obtained from CTTC.(17)

Statistical methods

Summary statistics and plots for individual trials were generated using SAS 9.4.

Meta-analytic models of post-trial data were built using STATA (version 14.2).

We built post-trial relative risk meta-analytic models for CVD mortality and all-cause mortality using reported number of events and number at risk for the post-trial period. Our principal summary measures for the models were relative risk and hazard ratios. We used adjusted relative risks where these were reported, and calculated unadjusted relative risks where they were not. We built random effects models for the analysis. We assessed the hetereogeneity of results using visual inspection of forest plots and I^2 statistics, and we conducted exploratory subgroup analysis using meta-regression to compare primary and secondary prevention trials. For the subgroup analysis, we tested for subgroup differences using a permutation test with 1000 permutations(18).

We also built hazard ratio meta-analytic models for CVD mortality and all-cause mortality where these were reported in the primary studies. We undertook sensitivity analysis by restricting the model to primary prevention trials.

Results

We identified 21 placebo-controlled RCTs of statins included in the CTTC for forward citation searching(19-39) which retrieved 1353 abstracts (restricting search to reports which included an original trialist as an author). We identified a further 1,802 abstracts from Medline and Embase (searches to 16 June 2016), and after excluding duplicates, 1520 titles and abstracts were screened. We retrieved 61 papers for full text review, 47 of which did not meet our selection criteria (eFigure). Reference searching of the remaining 14 studies identified one further study. Seven of the 15 studies used overlapping data: for each set of potentially overlapping reports, we chose the most recent report. This resulted in eight studies finally included in our review (eTable 1).

The original RCTs ranged in mean duration from 3.2 to 5.2 years, included trials of simvastatin, pravastatin, fluvastatin and atorvastatin, and their primary results were published between 1994 and 2003. Of the randomised participants in each trial, 0 to 52% were women, the mean age ranged from 50 to 75 years, and 1 to 35% were diabetic. Between 8 and 100% had pre-existing CVD: three predominantly primary prevention/asymptomatic populations, and five predominantly secondary prevention/symptomatic populations. The difference in the proportion of people taking a statin in the randomised groups within the trial period (statin – placebo) ranged from 51% to 89%. Hazard ratios (or relative risk ratio estimates when hazard ratios were unknown) for all-cause mortality and CVD-specific mortality within the trial period ranged from 0.70 to 1.02, and 0.64 to 0.96 respectively (eTable 2).

The post-trial follow up ranged in mean duration from 1.6 to 15.1 years. The difference in proportion of people taking a statin in the post-trial period (for those originally randomized to statin minus those randomized to placebo) ranged from 0 to 4% (unknown for two studies). Collectively, the included studies reported on post-trial follow-up of 55,732 people with 13,781 deaths which occurred after the trials ended, of which 6,685 were attributed to CVD. The hazard ratios (or relative risk estimates) for all-cause mortality and CVD-specific mortality ranged from 0.85 to 1.03, and 0.82 to 1.14 respectively (eTable 3).

Individual trials – comparison of within trial and post-trial effects

The results for CVD specific mortality for the individual trials are presented in Table 2 and Fig 2A. Of the 8 included trials, the six which demonstrated significant reductions in CVD mortality within the trial period (WOSCOPS, ALERT, SSSS, PROSPER, HPS and LIPID), showed less benefit in the post-trial period. The two trials without significant reduction in CVD mortality within the trial period (ALLHAT-LLA and ASCOT-LLA) showed a similar lack of benefit post-trial. In only one of the 8 trials was there a significant reduction in CVD mortality for the post-trial period (WOSCOPS).

The results for all-cause mortality for the individual trials are presented in eTable 3 and Fig 2B. Of the 8 included trials, the four which demonstrated significant reduction in all-cause mortality within the trial period (WOSCOPS, SSSS, HPS and LIPID) showed less benefit in the post-trial period. Three trials without a significant reduction in mortality within the trial period (ALLHAT-LLA, ALERT and PROSPER) showed a similar lack of benefit post-trial. One trial (ASCOT-LLA) without a significant reduction in mortality with the trial period demonstrated more benefit in the post-trial period. In only two of the 8 trials was there a significant reduction in all-cause mortality in the post-trial period (WOSCOPS and ASCOT-LLA).

Post-trial meta-analysis

The relative risk random effect meta-analysis using post-trial data from all eight studies is presented in Fig 3A (CVD mortality) and 3B (all-cause mortality). Although there was no evidence overall of a post-trial (legacy) effect on CVD (p=0.15), there was some evidence of a legacy effect on all-cause mortality (p=0.01). In the exploratory sub-group analysis there appeared to be a difference in the post-trial (legacy) effect of statins for primary prevention compared with secondary prevention studies for both CVD and for all-cause mortality. The pooled relative risk of CVD death post-trial for those originally allocated statin compared to placebo was 0.91 (0.84-0.98) for primary prevention trials, and 0.99 (0.94-1.05) for secondary prevention trials (permutation test p-value for sub-group difference=0.15) (Fig 3A). The pooled relative risk of all-cause death post-trial for those originally allocated statin compared to placebo was 0.92 (0.88-0.96) for primary prevention trials and 0.99 (0.95-1.03) for secondary prevention trials (permutation test p-value for sub-group difference=0.02) (Fig 3B).

The hazard ratio meta-analysis, using post-trial data from the 4 studies reporting hazard ratios, is presented in Fig 4A (CVD mortality) and 4B (all-cause mortality). Similar to the meta-analysis of relative risks, there was no definite evidence of a post-trial (legacy) effect on CVD (p=0.09), but some evidence of a legacy effect on all-cause mortality (p=0.02). Pooling data from all four studies resulted in substantial heterogeneity between studies (I-squared=40.7% for CVD mortality and 42.3% for all-cause mortality). Restricting meta-analysis to the three primary prevention trials resulted in very low heterogeneity between studies (I-squared=0.0% for CVD mortality and 8.1% for all-cause mortality), and these results are presented in Fig 4C (CVD mortality) and 4D (all-cause mortality). In the three

primary prevention trials, the pooled hazard ratio for CVD death post-trial for those originally allocated statin compared to placebo was 0.87 (0.79 to 0.95, p=0.003) and for all-cause death it was 0.90 (0.85to 0.96, p=0.001).

Discussion

We identified eight large randomized trials which had usable post-trial data to assess legacy effects. The direct effects of the statins on mortality reduction observed during the trials, were much larger than potential legacy effects observed post-trial, which suggests the rhetoric on legacy effects for statins in general may not reflect the empirical evidence. WOSCOPS was the only trial to show a possible post-trial legacy effect on all-cause and CVD specific mortality. When we pooled data from all eight studies we found no evidence overall of legacy effects on CVD mortality, but some evidence of legacy effects on all-cause mortality. In the exploratory sub-group analysis, there was some evidence of a difference in results for primary prevention compared with secondary prevention. Considering these subgroups separately, we found evidence of post-trial legacy effects only where statins were started for primary prevention – these effects were observed on both CVD mortality (HR=0.87, p=0.003) and all-cause mortality (HR=0.90, p<0.001) (Fig 4C and 4D). Participants originally randomised to placebo in two of the primary prevention trials (WOSCOPS and ASCOT-LLA) had 4% lower rates of using a statin in the first years post-trial, which will exaggerate the estimated legacy effect (bias away from the null), but this difference is unlikely to account for all the observed post-trial benefit (whether there was a difference in statin use post-trial in ALLHAT is not known). The observed post-trial reductions in CVD and all-cause mortality may potentially represent real legacy effects of statins for populations similar to those at the time of recruitment into these studies. There may be a higher likelihood of observing legacy

effects for statins when this is started for primary prevention, rather than for secondary prevention.

Our sensitive search strategy means this study is likely to have included all follow-up reports of the major placebo controlled statin trials, including recent follow-up reports for two of the studies (WOSCOPS and LIPID). Although we believe the post-trial period is the best period to analyse for detection of legacy effects, these data are no longer a randomised comparison: some patients randomised to the statin would have been saved from dying, whereas some patients in the placebo group were not. Hence, there are additional survivors in the statin group at the beginning of post-trial follow-up who are also likely to be at higher risk of CVD than survivors in the placebo group. These differences would tend to bias our results towards the null, and mean that legacy effects may be larger than we estimated. The main limitation of our report is that because our findings are based on aggregate data, we are unable to assess the effects of whether or not an individual was treated with statins during the post-trial period, and for how long, as well as their cardiovascular risk factor levels and other confounders.

We did not examine evidence of possible legacy effects on other outcomes such as non-fatal CVD, or for different post-trial follow-up times within each study, or for the same post-trial follow-up times between studies. We are aware of four other meta-analyses of data from long term follow-up after placebo controlled trials of lipid lowering treatment.(40-43) In three of these reports, the focus appears to have been on persistence of survival benefit, with comparison of event rates from time of randomisation, rather than post-trial legacy effect.(40, 42, 43) The other meta-analysis reported separate results for the post-trial period using data from earlier follow-up reports of six of our included trials.(41) That report found evidence of

post-trial reduction in CVD mortality and all-cause mortality at two years, and evidence for a reduction in major coronary events at both two years and over the total post-trial periods. The authors did not explore possible causes of heterogeneity for the post-trial models such as whether the primary trial was for primary or secondary prevention.

Published trial evidence supports the hypothesis that lowering cholesterol with a statin drug reduces cardiovascular events.(44) Currently, the principle of using absolute risk to guide treatment decisions (as recommended by guidelines(45-48)) is that treatment is prioritised for those at highest short term risk, and people at low short term risk are not treated. Data on the efficacy and safety of statins has led to treatment thresholds being lowered: in the UK the threshold was lowered from >20% to >10% ten-year risk of CVD; in the US the threshold is 10% ten-year risk of CVD, with statins also recommended for selected patients with 7.5-10% ten-year risk.(48) However, as short term risk is largely driven by age, younger people are unlikely to qualify for statins even with these lowered thresholds. For example, a recent report found that in the absence of smoking or raised blood pressure, a ten-year risk of CVD above 5% was infrequent in women younger than 50 and men younger than 40 years resident in the US.(49) Exploratory subgroup analysis in our study found possible legacy effects of statins following the primary prevention trials, which warrant further investigation. However, we note that the participants in WOSCOPS, ALLHAT and ASCOT-LLA had elevated levels of CVD risk factors (see table 1). Indeed, the majority of these people were likely to have been well above current treatment thresholds at the time of trial entry, and people with similar risk levels would now be recommended to start life-long lipid lowering treatment. Legacy effects in this setting serve to emphasise the benefits of starting primary prevention treatment early rather than later among people at high short term risk. It does not provide evidence to

support earlier treatment for people who have lower short term risk than current treatment thresholds.

"Legacy effects" have been explained as the "memory of a treatment given in an early phase of a disease which produces benefits long after the cessation of intervention".(2) They are an extension of the belief that we should intervene with treatment early on in the course of a chronic disease/condition; the legacy effect assumes that the duration of the condition predicts permanent pathological changes which in turn are strong modifiers of treatment effectiveness. This paradigm has some support from the finding that statins have minimal effect on CVD prevention in patients with advanced kidney disease who require haemodialysis, and who have high short term risk of CVD, (50) but reduce CVD events in patients with earlier chronic kidney disease who are not yet requiring haemodialysis.(51) There are also some data from a small imaging study of patients with angina to support the early treatment hypothesis, where similar reduction in lipid levels appeared to result in reduction in plaque volume only in participants younger than 65 years.(52) In both of these examples, the comparison is intervening early vs later in patients with clinical disease (chronic kidney disease or angina), and few would argue against early treatment in these clinical populations. Our findings suggest there may be a similar case for intervening early rather than later for those without clinical disease who have a high calculated short term risk of CVD. Advocates of early intervention argue that people who are at risk of disease in the long term, but currently displaying no symptoms or signs of disease and at low calculated short term risk, should also be started on treatment early.(5, 15) But deciding when, and if, to intervene in these people is much less straight forward.

The legacy effect hypothesis for statins - that the earlier you start , the lower your risk of a CVD event in the long term- has not been tested directly in a RCT comparing statins commencement at an earlier versus later age, and such a trial is unlikely to eventuate. Indirect evidence from post-trial follow-up after the large statin trials is likely the next best way to investigate this. In this analysis of 8 long-term randomized trials, we found possible post-trial legacy effects of statins on CVD mortality and all-cause mortality for primary prevention. Although the post-trial relative benefits were clearly smaller than those observed within trials, the increasing risk with age may mean that the absolute benefits are similar. Analysis of individual patient data from follow-up studies after placebo similar RCTs in lower risk populations may provide more definitive evidence on whether early treatment of subclinical atherosclerosis is likely to be beneficial.

Authors contributions

Agnish Nayak acquired, analysed and interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Andrew Hayen undertook the main statistical analysis, interpreted the data, critically revised the manuscript for important intellectual content and approved the final version.

Lin Zhu acquired, analysed and interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Kevin McGeechan interpreted the data, critically revised the manuscript for important intellectual content and approved the final version.

Paul Glasziou interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Les Irwig obtained funding, interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Jenny Doust interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Gabriel Gregory interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Katy Bell obtained funding, conceived the study and design, acquired, analysed and interpreted the data:, supervised the study, drafted the manuscript and revised for important intellectual content and approved the final version. She had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Figures

Fig 1. Survival and Hazard curves using simulated data where there is no legacy effect.

1A: Survival Curves; 1B: Hazard Curves

During RCT period (5 years): Relative Risk Reduction for CVD mortality=0.80; during post-trial period (20 years): Relative Risk Reduction for CVD mortality =1 (i.e. no legacy effect).

A persistent benefit is observed in the Survival Curve which is due entirely to the within-trial treatment effect. The lack of a post-trial legacy effect is more clearly shown in the Hazard Curve.

Fig 2. Direct (within-trial) and legacy (post-trial) effects of statins

2A: CVD mortality; 2B: All-cause mortality.

Fig 3. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins

3A: CVD mortality; 3B: All-cause mortality

Fig 4: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins

4A: CVD mortality for 4 trials; 4B: All-cause mortality for 4 trials; 4C: CVD mortality for 3 primary prevention trials; 4D: All-cause mortality for 3 primary prevention trials

Fig 1A. Survival curves using simulated data where there is no legacy effect.

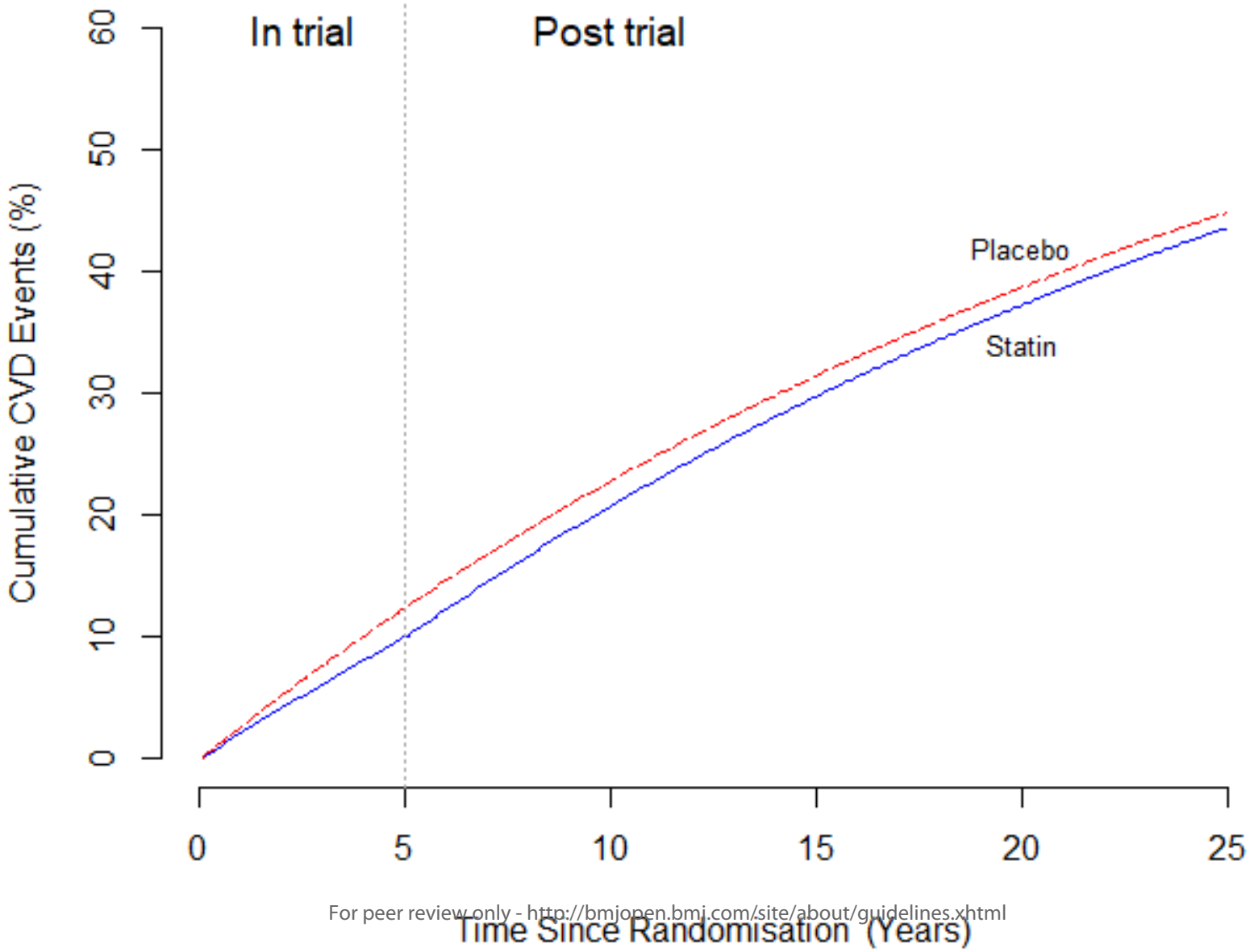


Fig 1B. Hazard curves using simulated data where there is no legacy effect.

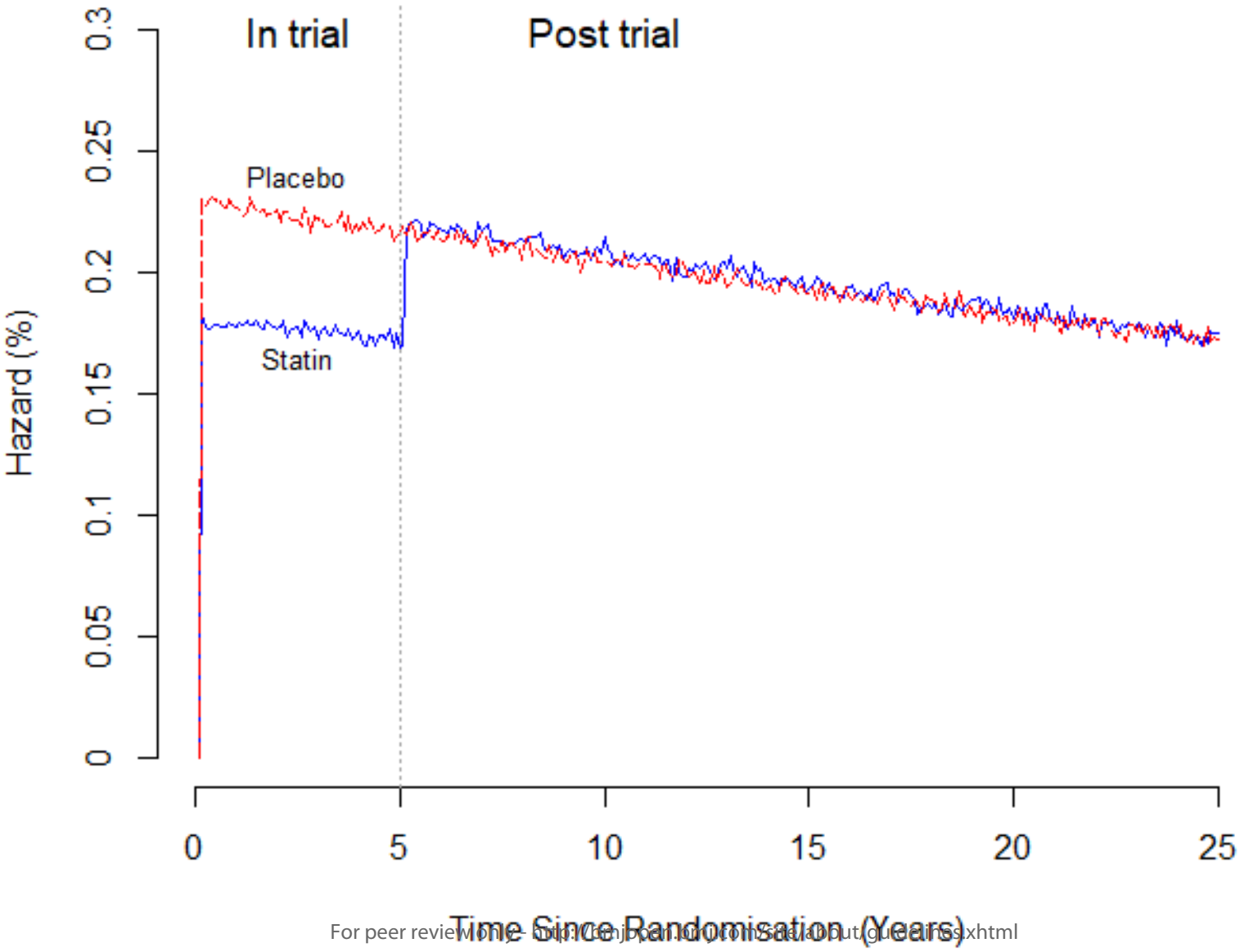


Fig 2A. Direct (within-trial) and legacy (post-trial) effects of statins on CVD mortality

Study (Initial Year of Randomisation)	n (events) Active	n (events) Placebo	Follow Up (years)	Proportion On Statins (%) Active	Proportion On Statins (%) Placebo
ALLHAT-LLT (1994)					
Within-trial	5089(529)	5110(546)	4.8	89	9.8
Post-trial	4428(484)	4432(511)	4		
ASCOT-LLA (1998)					
Within-trial	5168(74)	5137(82)	3.3	87	9
Post-trial	2234(377)	2198(430)	8.3	67	63
WOSCOPS (1989)					
Within-trial	3302(49)	3293(71)	4.9	70	0
Post-trial	3196(364)	3158(423)	15.1	39	35
ALERT (1996)					
Within-trial	1050(66)	1052(73)	5.4	85	14
Post-trial	819(22)	833(25)	1.6	78	78
SSSS (1988)					
Within-trial	2221(136)	2223(207)	5.4	90	2
Post-trial	2039(155)	1967(128)	5	86	82
PROSPER (1997)					
Within-trial	2891(122)	2913(154)	3.2	94	5
Post-trial	2588(396)	2600(375)	5.4		
HPS (1994)					
Within-trial	10269(826)	10267(998)	5.3	85	17
Post-trial	8863(1019)	8656(1007)	5.7	74	74
LIPID (1990)					
Within-trial	4512(331)	4502(433)	6	81	24
Post-trial	3932(756)	3789(765)	10	85	84

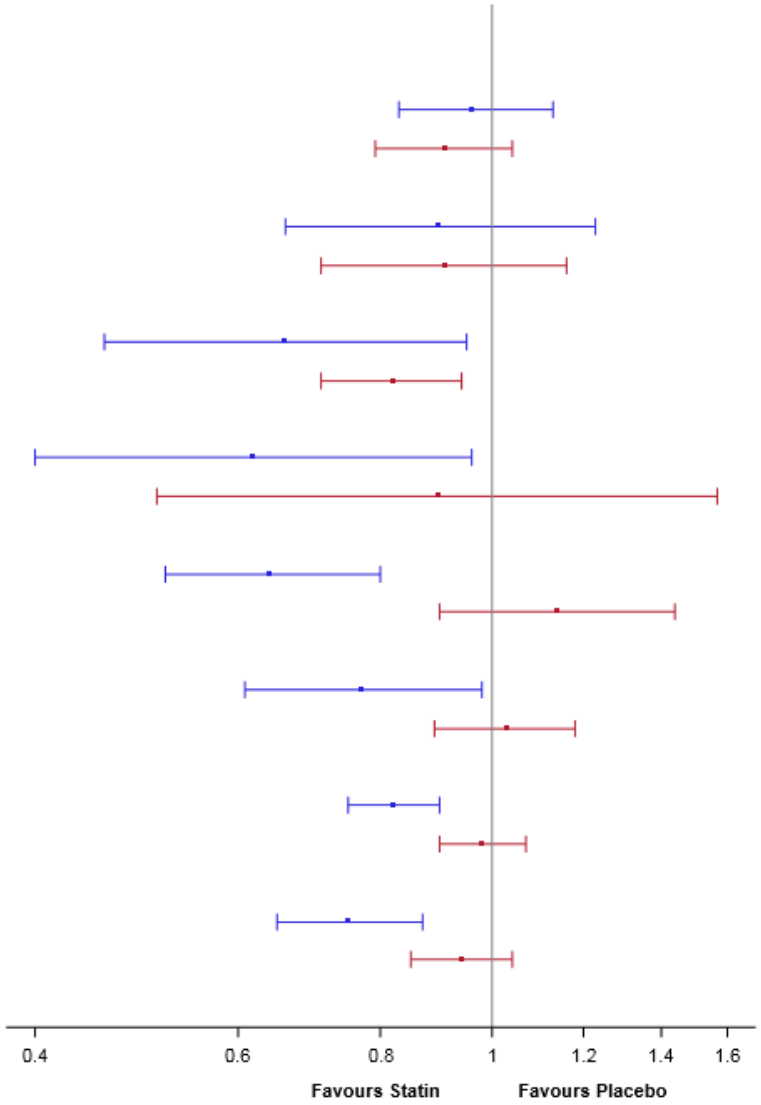


Fig 2B. Direct (within-trial) and legacy (post-trial) effects of statins on All cause mortality

Study (Initial Year of Randomisation)	n (events) Active	n (events) Placebo	Follow Up (years)	Proportion On Statins (%) Active	Proportion On Statins (%) Placebo
ALLHAT-LLT (1994)					
Within-trial	5089(661)	5110(678)	4.8	89	9.8
Post-trial	4428(897)	4432(948)	4		
ASCOT-LLA (1998)					
Within-trial	5168(185)	5137(212)	3.3	87	9
Post-trial	2234(377)	2198(430)	8.3	67	63
WOSCOPS (1989)					
Within-trial	3302(106)	3293(135)	4.9	70	0
Post-trial	3196(1036)	3158(1117)	15.1	39	35
ALERT (1996)					
Within-trial	1050(143)	1052(138)	5.4	85	14
Post-trial	819(51)	833(51)	1.6	78	78
SSSS (1988)					
Within-trial	2221(182)	2223(256)	5.4	90	2
Post-trial	2039(232)	1967(212)	5	86	82
PROSPER (1997)					
Within-trial	2891(298)	2913(306)	3.2	94	5
Post-trial	2588(931)	2600(928)	5.4		
HPS (1994)					
Within-trial	10269(1328)	10267(1507)	5.3	85	17
Post-trial	8863(1962)	8656(1949)	5.7	74	74
LIPID (1990)					
Within-trial	4512(498)	4502(633)	6	81	24
Post-trial	3932(1341)	3789(1319)	10	85	84

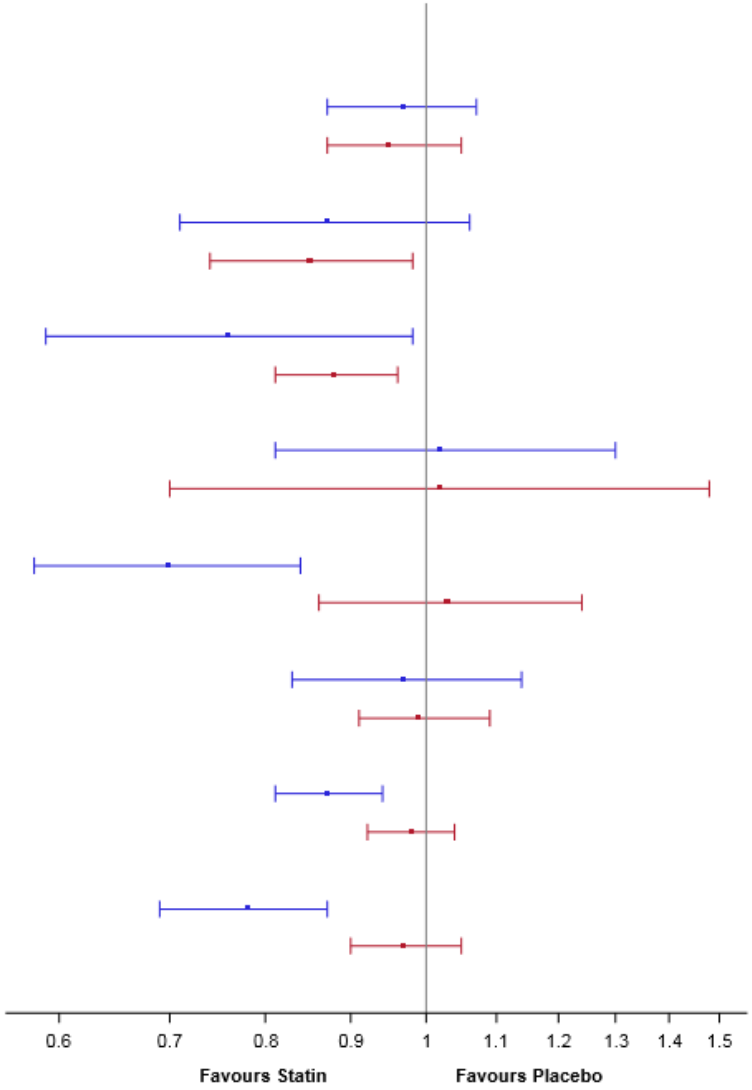


Fig 3A. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins on CVD mortality

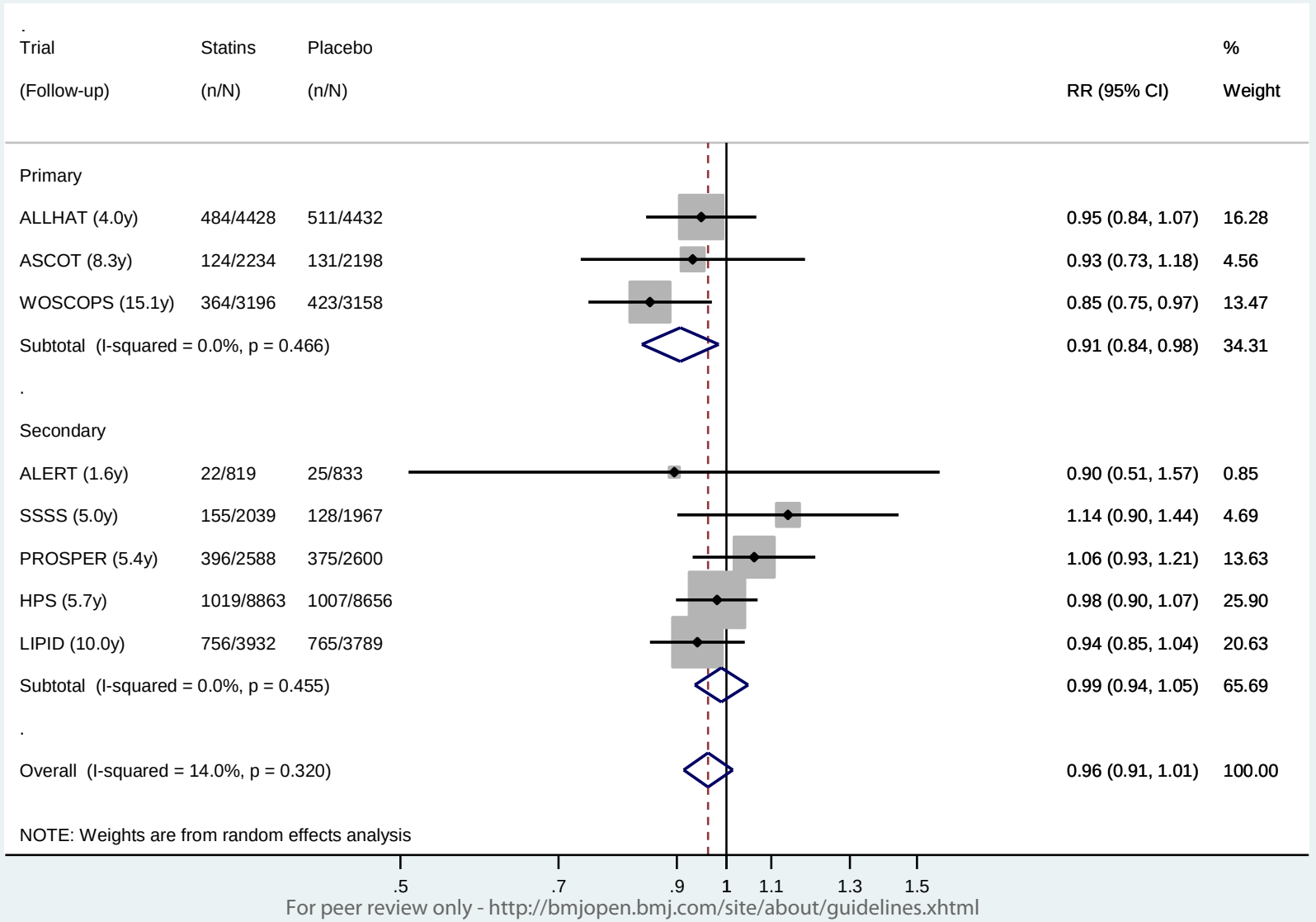


Fig 3B. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins on All cause mortality

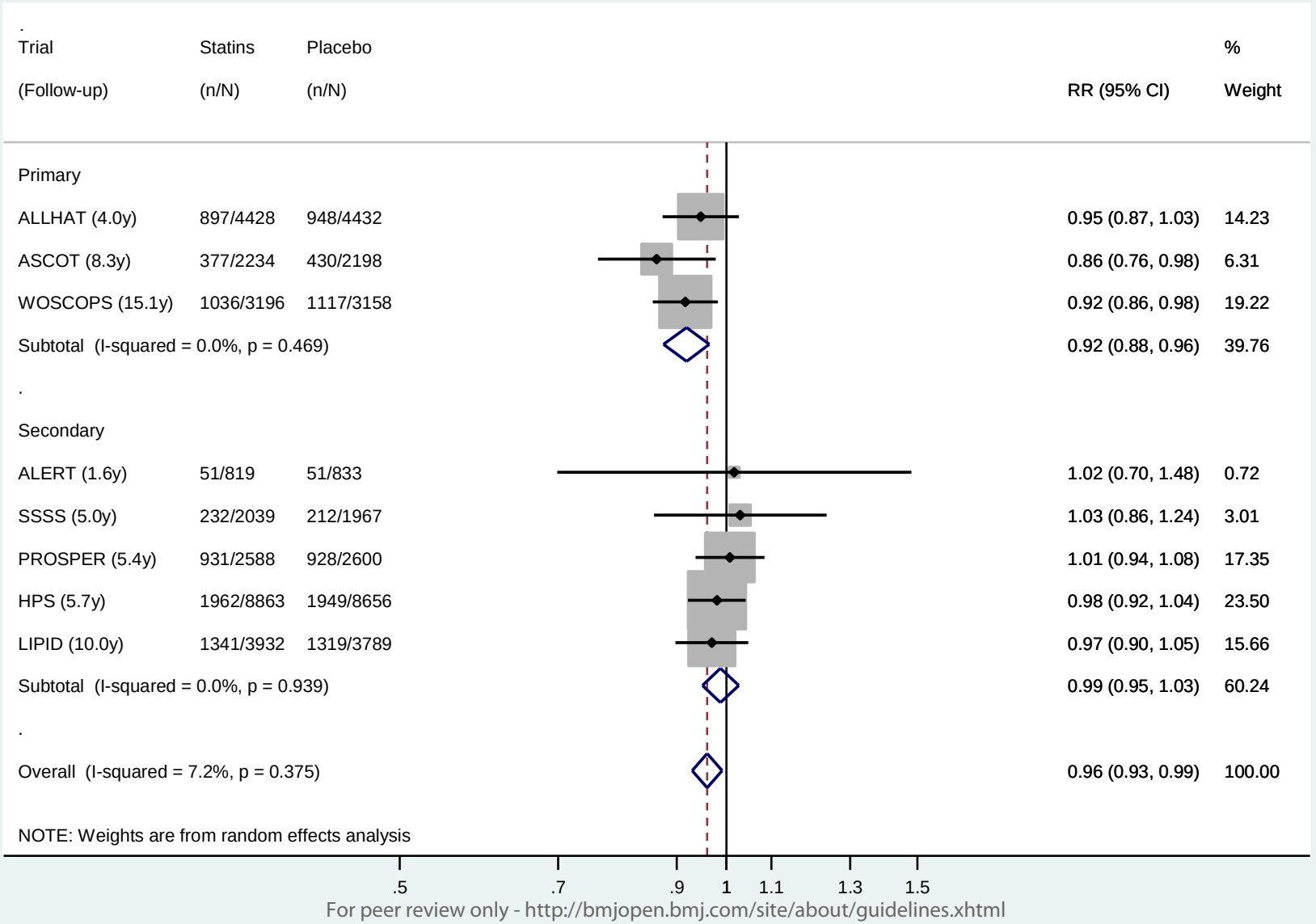


Fig 4A. Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on CVD mortality for 4 trials

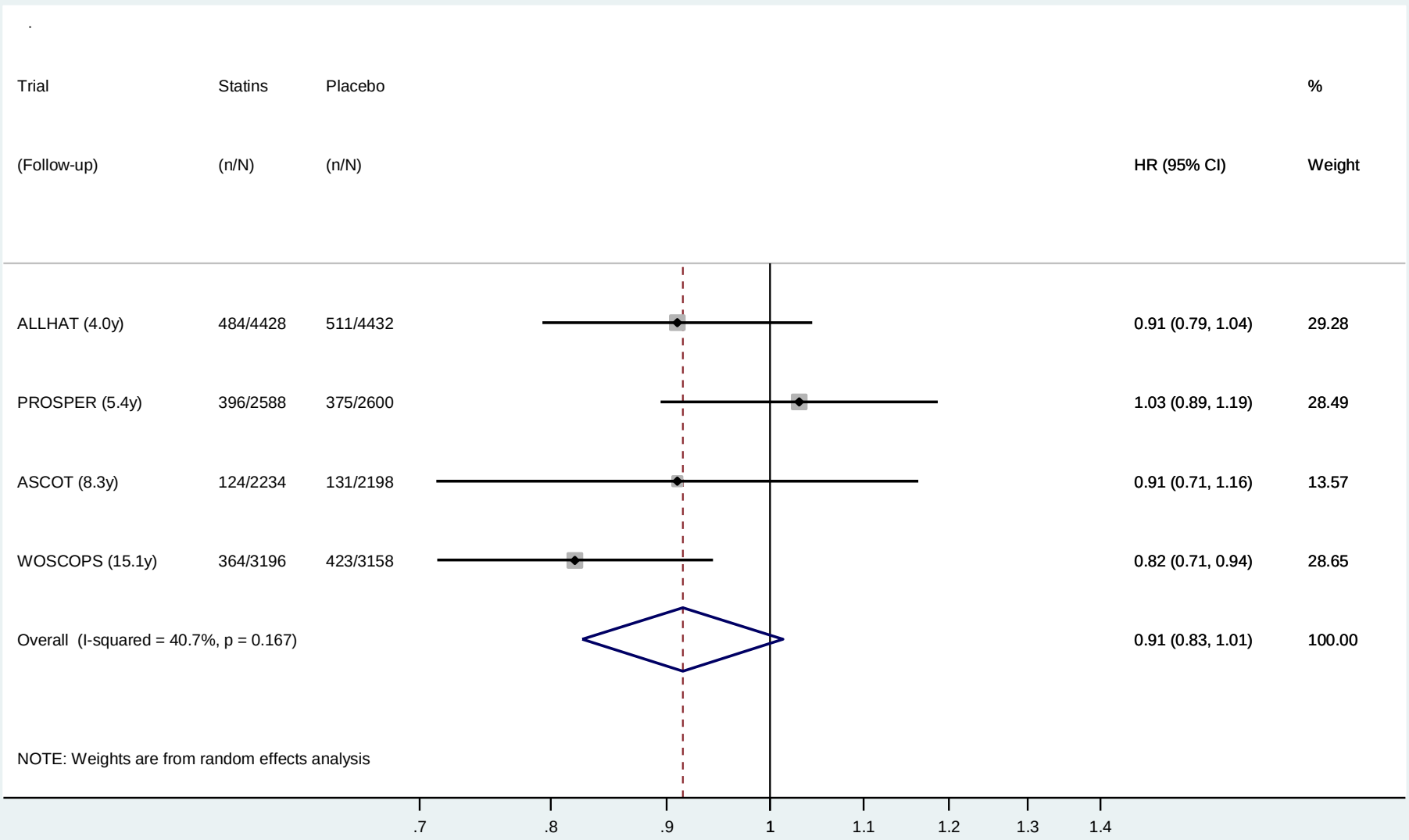


Fig 4B. Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on All cause mortality for 4 trials

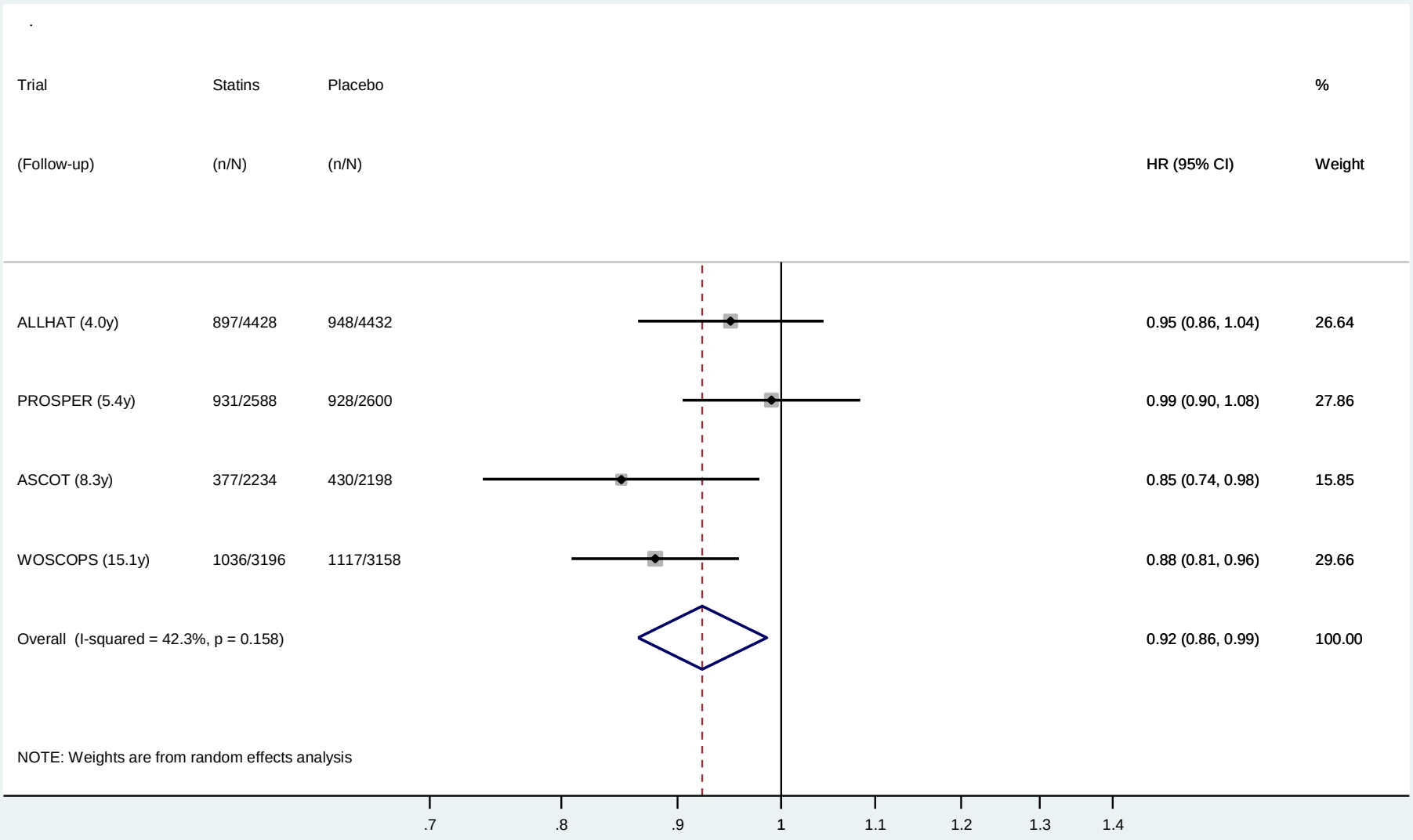


Fig 4C. Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on CVD mortality for 3 primary prevention trials

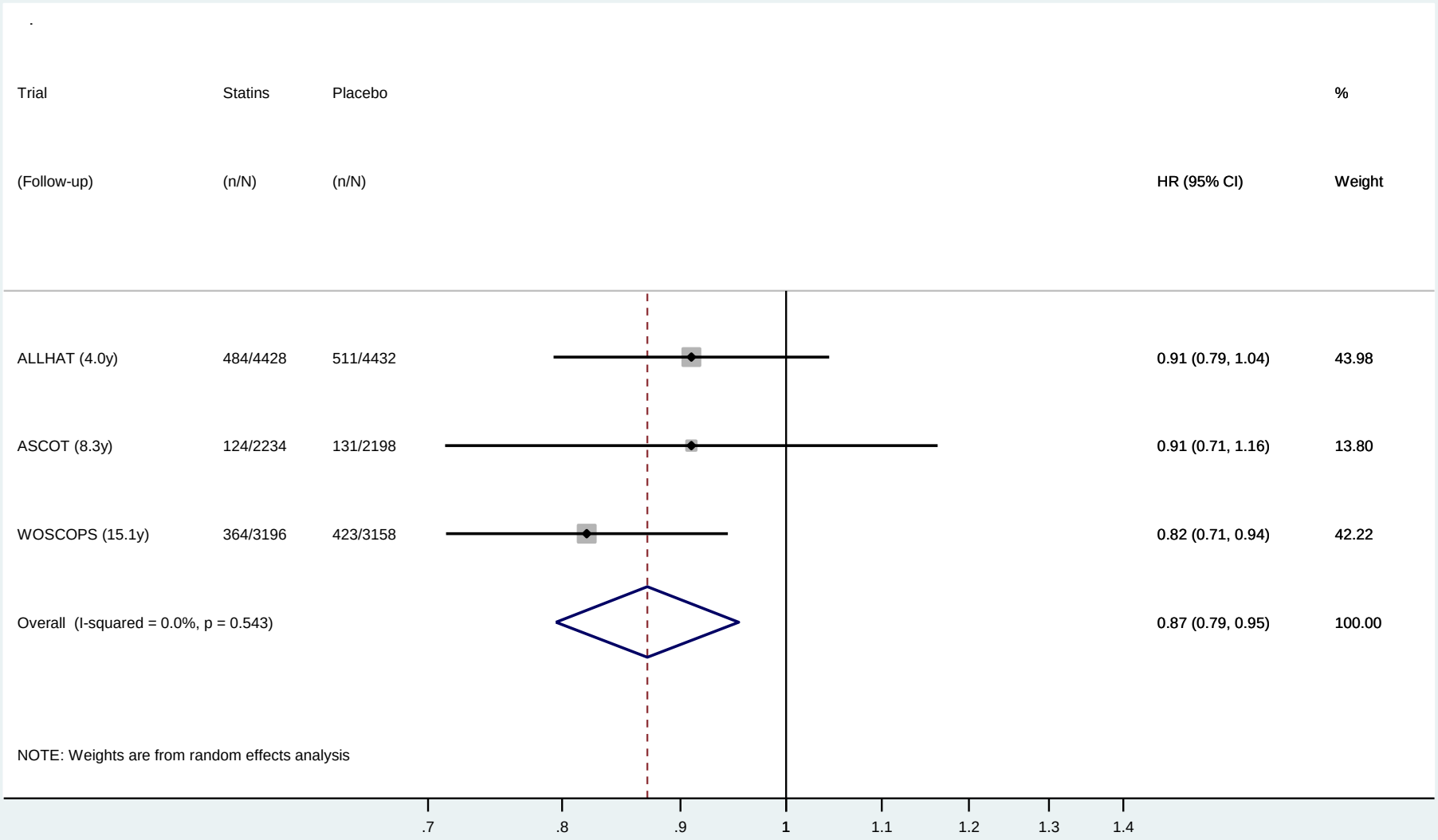
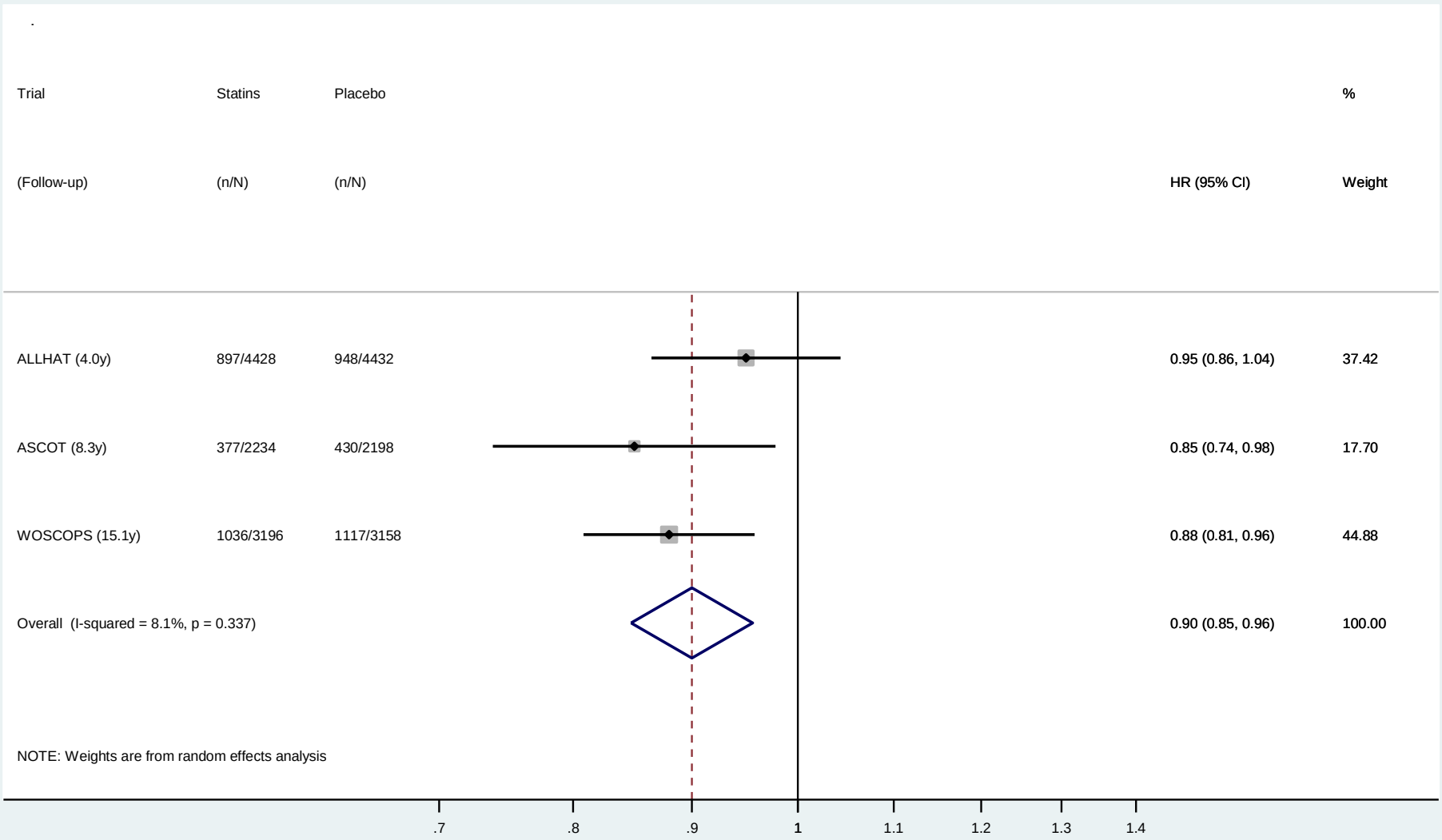


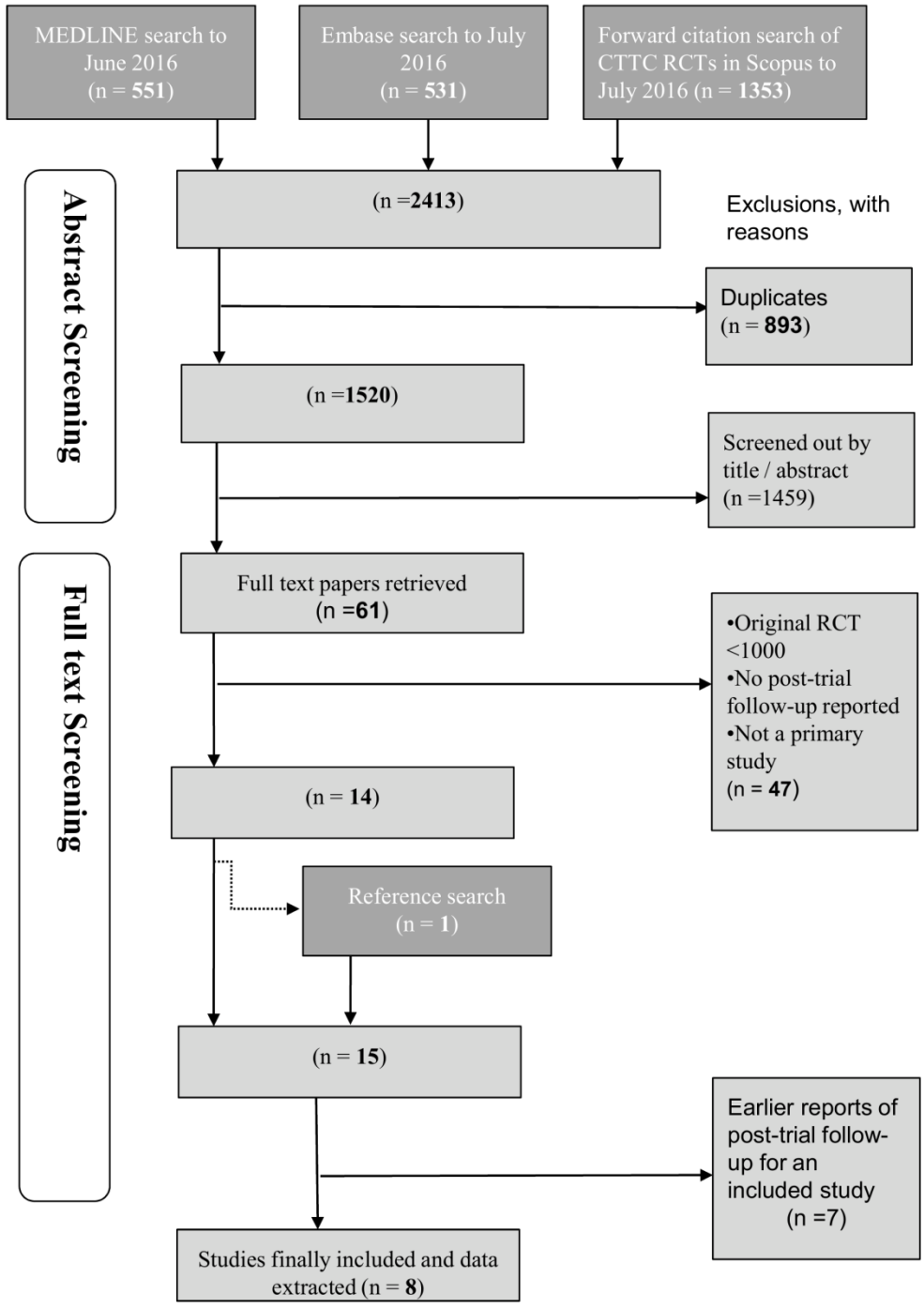
Fig 4D. Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on All cause mortality for 3 primary prevention trials



Simulation

We simulated outcomes for 4,000 people with equivalent pre-trial five-year CVD risk estimates for those who were randomized to have a statin or placebo. First, we set our simulation to include 2,000 people with baseline five-year risk of CVD mortality of 5% (high risk group) and 2,000 people with five-year risk of CV mortality of 1% (low risk group). Second, within the two risk groups we randomized individuals to statin or placebo at a ratio of 1:1. Third, we applied a relative risk reduction on CVD mortality of 0.80 for individuals randomized to statin for the five years of the trial period. After the trial, survivors in the group randomized to statin returned to their baseline five year risk of CVD mortality, and all individuals were followed until they had an event, up to a further 20 years. For simplicity, we did not include any effects for aging in the model. The simulation was run 1000 times in R 3.3.1. Survival and hazard curves were generated by calculating the average results.

eFigure. Selection of primary studies



CTTC = Cholesterol Treatment Trialists' Collaboration

eTable 1. Characteristics of the 8 included studies

Study	Target population	Dates of recruit-ment	Mean follow-up (years)	Statin	Number of participants	Proportion of women (%)	Mean age (range, years)	Diabetes (%)	History of CVD (%)	Duration of post-trial follow-up	Difference in proportion taking statins post-trial (%)
Primary Prevention/ Primary care population											
ALLHAT-LLT	Treated for high BP with high cholesterol	1994-1998	4.8	Pravastatin 40mg	10355	49	66 (55-?)	35	11	4	?
ASCOT-LLA	High BP and no history of CHD, with 3+ other CVD risk factors	1998-2000	3.2	Atorvostatin 10mg	10305	19	63 (40-79)	25	14	8.3	4
WOS-COPS	Men with high cholesterol and no history of myocardial infarction	1989-1991	4.8	Pravastatin 40mg	6595	0	55 (45-64)	1	8	15.1	4
Secondary Prevention/ Clinical population											

ALERT	Renal or combined renal and pancreas transplant recipients at high risk of CVD	1996-1997	5.1	Fluvastatin 40mg	2102	34	50 (30-75)	19	19	1.6	0
SSSS	History of angina or myocardial infarction	1988-1989	5.2	Simvastatin 20-40mg	4444	19	60+ (35-70)	5	100	5	4
PROSPER	≥70 years with history of CVD or at high risk of CVD	1997-1999	3.2	Pravastatin 40mg	5804	52	75 (70-82)	11	44	5.4	?
HPS	Coronary disease, other occlusive arterial disease, diabetes or treated for high BP	1994-1997	5.0	Simvastatin 40mg	20536	25	64 (40-80)	29	85	5.7	0
LIPID	Myocardial infarction or hospitalization for unstable angina	1990-1992	5.6	Pravastatin 40mg	9014	17	62 (31-75)	9	>99	10	1

Notes

1. CVD = Cardiovascular Disease
2. Order of trials within primary prevention and secondary prevention order is from shortest post-trial follow-up to longest.

eTable 2 Effect of treatment allocation on All-cause mortality and CVD-mortality reported within trial period

Study	Difference in proportion taking statins within-trial (%)[1]	Allocated to statins			Allocated to placebo			Risk Estimates	
		N	All deaths	CVD deaths	N	All deaths	CVD deaths	All deaths	CVD deaths
ALLHAT-LLT	79	5089	661	529	5110	678	546	0.97 (0.87-1.07)[2]	0.96 (0.83-1.13)[2]
ASCOT-LLA	78	5168	460	154	5137	520	167	0.87 (0.71-1.06)[2]	0.90 (0.66-1.23)[2]
WOS-COPS	70	3302	106	49	3293	135	71	**0.76 (0.59-0.98)[2]**	**0.66 (0.46-0.95)[2]**
ALERT	71	1050	143	66	1052	138	73	1.02 (0.81-1.30)[3]	**0.62 (0.40-0.96)[3]**
SSSS	88	2221	182	136	2223	256	207	**0.70 (0.58-0.84)[3]**	**0.64 (0.52-0.80)[3]**
PROSPER	89	2891	298	122	2913	306	154	0.97 (0.83–1.14)[2]	**0.77 (0.61–0.98)[2]**
HPS	68	10269	1328	826	10267	1507	998	**0.87(0.81-0.94)[3]**	**0.82 (0.75-0.90)[3]**
LIPID	57	4512	498	331	4502	633	433	**0.77 (0.69-0.87)[3]**	**0.75 (0.65-0.87)[3]**

Notes

1. Difference in % taking statins = [% taking statins in group allocated to statin in trial - % taking statins in group allocated to placebo in trial]
2. Studies reporting Hazard Ratio
3. Studies reporting Relative Risk
4. Statistically significant results are **bolded**
5. CVD = Cardiovascular Disease
6. Order of trials within primary prevention and secondary prevention is from shortest post-trial follow-up to longest.

eTable 3 Effect of treatment allocation on All-cause mortality and CVD-mortality reported for post-trial period

Study	Average post-trial follow-up	Difference in proportion taking statins post-trial (%)[1]	Allocated to statins			Allocated to placebo			Risk Ratio	
			N[4]	All deaths	CVD deaths	N[4]	All deaths	CVD deaths	All deaths	CVD deaths
ALLHAT-LLT	4	?	4428	897	484	4432	948	511	0.91 (0.79–1.04)[2]	0.95 (0.87-1.05)[2]
ASCOT-LLA	8.3	4	2234	377	124	2198	430	131	**0.85 (0.74-0.98)**[2]	0.91 (0.71-1.16)[2]
WOS-COPS	15.1	4	3196	1036	364	3158	1117	423	**0.88 (0.81-0.96)**[2]	**0.82 (0.71-0.94)**[2]
ALERT	1.6	0	811	51	22	820	51	25	1.01 (0.69 - 1.47)[3]	0.89 (0.51 - 1.56)[3]
SSSS	5	4	2039	232	155	1967	212	128	1.03 (0.86-1.24)[3]	1.14 (0.90-1.44)[3]
PROSPER	5.4	?	2588	931	396	2600	928	375	0.99 (0.91-1.09)[2]	1.03 (0.89-1.18)[2]
HPS	5.7	0	8863	1962	1019	8656	1949	1007	0.98 (0.90-1.07)[3]	0.98 (0.92-1.04)[3]
LIPID	10	1	3932	1341	756	3789	1319	765	0.97 (0.90-1.05)[3]	0.94 (0.85-1.04)[3]

Notes

1. Difference in % taking statins = [% taking statins in group allocated to statin in trial - % taking statins in group allocated to placebo in trial]
2. Studies reporting Hazard Ratio
3. Studies reporting Relative Risk
4. Number alive and followed post-trial
5. Statistically significant results are **bolded**
6. CVD = Cardiovascular Disease
7. Order of trials within primary prevention and secondary prevention is from shortest post-trial follow-up to longest

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 (Box 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	eFigure
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eTable 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10 eTables 2-3 Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11 Figures 3-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 Figures 3A, 3B, 4C,4D
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Legacy effects of statins on cardiovascular and all-cause mortality - A meta-analysis

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Legacy effects of statins on cardiovascular and all-cause mortality

- A meta-analysis

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ABSTRACT

Objectives: To assess evidence for "legacy" (post-trial) effects on cardiovascular (CVD) and all-cause mortality among adult participants of placebo controlled randomised trials (RCTs) of statins.

Design: Meta-analysis of aggregate data

Setting/Participants: placebo controlled statin RCTS for primary and secondary CVD prevention

Methods: Data Sources: PubMed, Embase from inception and forward citations of Cholesterol Treatment Trialists' Collaborators RCTs to 16th June 2016.

Study Selection: two independent reviewers identified all statin RCT follow-up reports including ≥1000 participants, and cardiovascular and all-cause mortality.

Data Extraction and Synthesis: Independent data extraction was done by two reviewers according to PRISMA guidelines.

Main Outcomes: post-trial CVD and all-cause mortality.

Results: We included 8 trials, with mean post-trial follow-up ranging from 1.6-15.1 years, and including 13,781 post-trial deaths (6,685 CVD). Direct effects within-trials were greater than legacy effects post-trials. The pooled data from all eight studies showed no evidence overall of legacy effects on CVD mortality, but some evidence of legacy effects on all-cause mortality (p=0.01). Exploratory subgroup analysis found possible differences in legacy effect for primary prevention trials compared to secondary prevention trials for both CVD mortality (p=0.15) and all-cause mortality (p=0.02). Pooled post-trial hazard ratios for the three primary prevention studies demonstrated possible post-trial legacy effects on CVD mortality (HR=0.87; 95% CI 0.79-0.95) and on all-cause mortality (HR=0.90; 95% CI 0.85-0.96).

Conclusions: Possible post-trial statin legacy effects on all-cause mortality appear to be driven by the primary prevention studies. Although these relative benefits were smaller than those observed within-trial, the absolute benefits may be similar for the two time periods. Analysis of individual patient data from follow-up studies after placebo controlled statin RCTs in lower risk populations may provide more definitive evidence on whether early treatment of subclinical atherosclerosis is likely to be beneficial.

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Keywords

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Strengths and limitations of this study

- Our sensitive search strategy means this study is likely to have included all follow-up reports of the major placebo controlled statin trials, including recent follow-up reports for two of the studies (WOSCOPS and LIPID).
- We focus analysis on the post-trial period which is best for detection of legacy effects,
- However post-trial data are no longer a randomised comparison, and legacy effects may be larger than we estimated.
- The main limitation is that our findings are based on aggregate data, and we did not have information on whether or not an individual was treated with statins during the post-trial period, and for how long, as well as their cardiovascular risk factor levels and other potential confounders.

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INTRODUCTION

'Legacy effects' are treatment effects that persist or emerge at some time after trial treatment ends. The existence, or not, of such legacy effects have important clinical implications, including the potential value of starting preventative treatment at a younger age, and the risks of treatment cessation. Although technically even short term or transient improvement or worsening of symptoms and signs may be classified as a legacy effect, most people appear to use the term to indicate sustained clinical benefit or harm.(1-7) Legacy effects have been explained as the "memory of a treatment given in an early phase of a disease which produces benefits long after the cessation of intervention".(2) They are an extension of the belief that we should intervene with treatment early on in the course of a chronic disease/condition; the legacy effect assumes that the duration of the condition predicts permanent pathological changes which in turn are strong modifiers of treatment effectiveness.

Recently there has been considerable interest in the possible legacy effects of statins,(8, 9) sparked by reports on the long term outcomes for participants of large placebo controlled trials. In some of these reports,(4, 10) there is still a persistent survival advantage to participants who were randomised to statin during the trial, even though there was no or minimal difference in the management of participants after the trial ended. Legacy effects could indicate that earlier treatment with statins slows atherosclerotic plaque build-up in arteries and so alters the natural disease progression during a person's lifetime. As with the direct effects of statins, these legacy effects may be pleiotropic, and act through anti-inflammation, anti-coagulation and or lipid lowering. This hypothesis has some support from the finding that statins have minimal effect on CVD prevention in patients with advanced kidney disease who require haemodialysis, and who have high short term risk of CVD, (11) but reduce CVD events in patients with earlier chronic kidney disease who are not yet requiring haemodialysis.(12) There are also some data from a small imaging study of patients

with angina to support the early treatment hypothesis, where similar reduction in lipid levels appeared to result in reduction in plaque volume only in participants younger than 65 years.(13) Finally, differences in long term response to statins are noted for primary prevention trials compared with secondary prevention trials.(14) To this end, aggressive lipid lowering therapy in much younger individuals with lower risk for cardiovascular disease has been suggested as a possible means of primary prevention. Some have argued for universal screening of cholesterol levels in young people and offering early statin treatment to those with raised levels,(15-17) whereas others have argued that statins be offered to all young people, regardless of cholesterol levels. (5, 18)

At least some of the survival benefit observed on long term follow-up is attributable to the direct treatment effects on cardiovascular disease outcomes observed during the within-trial period. To illustrate this point we generated data to simulate the situation where there was (eFigure 1A and 1B), and was not (eFigure 1C and 1D), a legacy effect (we simulated two scenarios where an intervention has effects during the trial period, and (i) has an effect after the trial (legacy effect) or (ii) has no effect after the trial (no legacy effect).In the survival curves of both scenarios the apparent legacy effect is exaggerated because the cumulative incidence includes the direct effects during the initial trial period (eFigure 1A and 1C). If hazard curves are constructed instead, the direct effects during the initial trial period are not included in the instantaneous hazard of the post trial periods, allowing an unbiased estimation of the legacy effect (eFigure 1B and ID; note that these are curves of the instantaneous hazard at each time point, and are not curves of hazard ratios. Details of the methods for the simulation are provided in the Appendix). Although survival curves like eFigure 1A and IC demonstrate that the direct effects of the intervention (observed during the trial period) are still apparent many years later, they do not provide evidence of legacy effects after the

intervention has ceased. From the hazard curves in eFigure 1B and 1D it is clear that to estimate legacy effects, we should instead focus on outcomes observed during the post-trial period. To this end, we aimed to identify and combine estimates of the effect of trial treatment group allocation on post-trial all-cause and CVD mortality from published reports on the long term follow-up after placebo controlled trials of statins.

METHODS

Protocol and Registration

The review protocol was not registered.

Selection

We performed a systematic search and meta-analysis of all reports on follow-up after randomized, placebo-controlled studies of adults (age >18 years) of statins with ≥1000 participants. As the legacy effect relates to the difference in treatment received within the trial period, we focused our analysis on follow up reports of high quality, large RCTs. We chose to limit our studies to those with ≥1000 participants in the original trial for consistency with the Cholesterol Treatment Trialists' Collaboration. These large trials were designed to assess effects on mortality within the trial period, and their follow-up reports are the most appropriate studies to address post-trial effects on mortality. We excluded studies that did not report mortality data during post-trial follow-up. The primary outcomes were death due to all-causes and due to cardiovascular disease.

Search strategy

We identified placebo controlled RCTs of cholesterol lowering treatment from the Cholesterol Treatment Trialists' Collaboration (19) and ran forward citation searches in Scopus; search was limited to those citations which included one of the investigators from the

RCT. We searched for additional reports in Medline and Embase with no earliest date restriction, though to 16th June 2016 using the terms listed in Box 1, with no restrictions on year published, type of publication, or language. We checked references of included studies to identify further relevant papers and contacted trialists to identify updated or additional reports.

Box 1: Search terms for Medline Search:

1 Follow-Up Studies/

2 random$.tw

3 placebo.tw

4 Hydroxymethylglutaryl-CoA Reductase Inhibitors/

5 cholesterol/

8 lipids/

10 (#1) AND (#2) AND (#3) AND (#4 OR #5 OR #6)

Validity assessment

Two authors (AN and LZ) extracted data for both within-trial and post-trial periods on the following characteristics which may bias the estimated legacy effect: Mean follow-up (years), Difference in proportion taking statins.

Study selection and data abstraction

Two authors (AN and KB) independently checked the titles and abstracts of all citations identified through the database searches and forward citation search. Full text was obtained if either author judged the article potentially relevant. The same two authors then independently checked all the full text articles for eligibility, resolving disagreements through discussion.

Two authors independently extracted clinical data (AN and LZ) using standardized forms, deciding disagreements through discussion with a third author (KB). We did not calculate formal measures of agreement to describe agreement between reviewers. The Cochrane Collaboration recommends against doing this, and instead recommends exploring reasons for any disagreement early on in the review process(20), which we did through discussion. We extracted separate data on all-cause mortality and CVD specific mortality for the within-trial and post-trial periods; the number of people at risk of each type of event at the start of the trial and at the start of the post-trial follow-up; the proportion of people taking statins within trial and post-trial; the duration of follow-up within trial and post-trial. We attempted to extract differences in mean total cholesterol, but these were missing for at least one of the periods in the majority of studies. Further data on the original trials was obtained from CTTC.(21)

Statistical methods

Summary statistics and plots for individual trials were generated using SAS 9.4.

Meta-analytic models of post-trial data were built using STATA (version 14.2).

We built meta-analytic models for CVD mortality and all-cause mortality using reported number of events and number at risk for the post-trial period. Our principal summary measures for the models were relative risk and hazard ratios. We used adjusted relative risks where these were reported, and calculated unadjusted relative risks where they were not. We built random effects models for the analysis. We assessed the hetereogeneity of results using visual inspection of forest plots and I^2 statistics, and we conducted exploratory subgroup analysis using meta-regression to compare primary and secondary prevention trials. For the

subgroup analysis, we tested for subgroup differences using a permutation test with 1000 permutations(22).

We also built hazard ratio meta-analytic models for CVD mortality and all-cause mortality where these were reported in the primary studies. We undertook sensitivity analysis by restricting the model to primary prevention trials.

Patient and Public Involvement

Patients and or public were not involved in this meta-analysis of published data.

RESULTS

We identified 21 placebo-controlled RCTs of statins included in the CTTC for forward citation searching(23-43) which retrieved 1520 abstracts (restricting search to reports which included an original trialist as an author). We identified a further 828 abstracts from Medline and Embase (searches to 16 June 2016), and after excluding duplicates, 1520 titles and abstracts were screened. We retrieved 61 papers for full text review, 47 of which did not meet our selection criteria (eFigure 2). Reference searching of the remaining 14 studies identified one further study. Seven of the 15 studies used overlapping data: for each set of potentially overlapping reports, we chose the most recent report. This resulted in eight studies finally included in our review (Table 1).

The original RCTs ranged in mean duration from 3.2 to 5.2 years, included trials of simvastatin, pravastatin, fluvastatin and atorvastatin, and their primary results were published between 1994 and 2003. Of the randomised participants in each trial, 0 to 52% were women,

the mean age ranged from 50 to 75 years, and 1 to 35% were diabetic. Between 8 and 100% had pre-existing CVD: three predominantly primary prevention/asymptomatic populations, and five predominantly secondary prevention/symptomatic populations. The difference in the proportion of people taking a statin in the randomised groups within the trial period (statin – placebo) ranged from 51% to 89%. Hazard ratios (or relative risk ratio estimates when hazard ratios were unknown) for all-cause mortality and CVD-specific mortality within the trial period ranged from 0.70 to 1.02, and 0.64 to 0.96 respectively (eTable 1).

The post-trial follow up ranged in mean duration from 1.6 to 15.1 years. The difference in proportion of people taking a statin in the post-trial period (for those originally randomized to statin minus those randomized to placebo) ranged from 0 to 4% (unknown for two studies). Collectively, the included studies reported on post-trial follow-up of 55,732 people with 13,781 deaths which occurred after the trials ended, of which 6,685 were attributed to CVD. The hazard ratios (or relative risk estimates) for all-cause mortality and CVD-specific mortality ranged from 0.85 to 1.03, and 0.82 to 1.14 respectively (eTable 2).

Individual trials – comparison of within trial and post-trial effects

The results for CVD specific mortality for the individual trials are presented in eTables 1 and 2, and Fig 1. Of the 8 included trials, the six which demonstrated significant reductions in CVD mortality within the trial period (WOSCOPS, ALERT, SSSS, PROSPER, HPS and LIPID), showed less benefit in the post-trial period than in the trial period. The two trials without significant reduction in CVD mortality within the trial period (ALLHAT-LLA and ASCOT-LLA) showed a similar lack of evidence for benefit post-trial. In only one of the 8 trials was there a significant reduction in CVD mortality for the post-trial period (WOSCOPS).

The results for all-cause mortality for the individual trials are presented in eTables 1 and 2, and Fig 2. Of the 8 included trials, the four which demonstrated significant reduction in all-cause mortality within the trial period (WOSCOPS, SSSS, HPS and LIPID) showed less benefit in the post-trial period than in the trial period. Three trials without a significant reduction in mortality within the trial period (ALLHAT-LLA, ALERT and PROSPER) showed a similar lack of evidence for benefit post-trial. One trial (ASCOT-LLA) without a significant reduction in mortality with the trial period demonstrated more benefit in the post-trial period. In only two of the 8 trials was there a significant reduction in all-cause mortality in the post-trial period (WOSCOPS and ASCOT-LLA).

Post-trial meta-analysis

The relative risk random effect meta-analysis using post-trial data from all eight studies is presented in Fig 3 (CVD mortality) and Fig 4 (all-cause mortality). Although there was no evidence overall of a post-trial (legacy) effect on CVD (p=0.15), there was some evidence of a legacy effect on all-cause mortality (p=0.01). In the exploratory sub-group analysis there appeared to be a difference in the post-trial (legacy) effect of statins for primary prevention compared with secondary prevention studies for both CVD and for all-cause mortality. The pooled relative risk of CVD death post-trial for those originally allocated statin compared to placebo was 0.91 (0.84-0.98) for primary prevention trials, and 0.99 (0.94-1.05) for secondary prevention trials (permutation test p-value for sub-group difference=0.15) (Fig 3). The pooled relative risk of all-cause death post-trial for those originally allocated statin compared to placebo was 0.92 (0.88-0.96) for primary prevention trials and 0.99 (0.95-1.03) for secondary prevention trials (permutation test p-value for sub-group difference=0.02) (Fig 4).

The hazard ratio meta-analysis, using post-trial data from the 4 studies reporting hazard ratios, is presented in Fig 5 (CVD mortality) and 6 (all-cause mortality). Similar to the meta-analysis of relative risks, there was no definite evidence of a post-trial (legacy) effect on CVD (p=0.09), but some evidence of a legacy effect on all-cause mortality (p=0.02). Pooling data from all four studies resulted in substantial heterogeneity between studies (I-squared=40.7% for CVD mortality and 42.3% for all-cause mortality). Restricting meta-analysis to the three primary prevention trials resulted in very low heterogeneity between studies (I-squared=0.0% for CVD mortality and 8.1% for all-cause mortality), and these results are presented in Fig 7 (CVD mortality) and Fig 8 (all-cause mortality). In the three primary prevention trials, the pooled hazard ratio for CVD death post-trial for those originally allocated statin compared to placebo was 0.87 (0.79 to 0.95, p=0.003) and for all-cause death it was 0.90 (0.85to 0.96, p=0.001).

DISCUSSION

We identified eight large randomized trials which had usable post-trial data to assess legacy effects on mortality outcomes. The direct effects of the statins on mortality reduction observed during the trials, were much larger than potential legacy effects observed post-trial, which suggests the rhetoric on legacy effects for statins in general may not reflect the empirical evidence. WOSCOPS was the only trial to show a possible post-trial legacy effect on all-cause and CVD specific mortality. When we pooled data from all eight studies we found no evidence overall of legacy effects on CVD mortality, but some evidence of possible legacy effects on all-cause mortality. In the exploratory sub-group analysis, there was some evidence of a difference in results for primary prevention compared with secondary prevention. Considering these subgroups separately, we found no evidence of legacy effects following secondary prevention trials, suggesting the importance of long term /life-long

prevention in these patients. We found evidence of possible post-trial legacy effects only where statins were started for primary prevention – these effects were observed on both CVD mortality (HR=0.87, p=0.003) and all-cause mortality (HR=0.90, p<0.001) (Fig 3C and 3D). Participants originally randomised to placebo in two of the primary prevention trials (WOSCOPS and ASCOT-LLA) had 4% lower rates of using a statin in the first years post-trial, which will exaggerate the estimated legacy effect (bias away from the null), but this difference is unlikely to account for all the observed post-trial benefit (whether there was a difference in statin use post-trial in ALLHAT is not known). The observed post-trial reductions in CVD and all-cause mortality may potentially represent real legacy effects of statins for populations similar to those at the time of recruitment into these studies. There may be a higher likelihood of observing legacy effects for statins when this is started for primary prevention, rather than for secondary prevention.

Our sensitive search strategy means this study is likely to have included all published follow-up reports of the major placebo controlled statin trials, including recent follow-up reports for two of the studies (WOSCOPS and LIPID). However we did not assess for publication bias and it is possible that unpublished follow-up reports may exist that we are unaware of. We did not assess risk of bias for the included studies, but this has been assessed by others for the original trial reports, including very recently(44), and the included studies were generally found to be high quality. Although we believe the post-trial period is the best period to analyse for detection of legacy effects, these data are no longer a randomised comparison: some patients randomised to the statin would have been saved from dying, whereas some patients in the placebo group were not. Hence, there are additional survivors in the statin group at the beginning of post-trial follow-up who are also likely to be at higher risk of CVD than survivors in the placebo group. These differences would tend to bias our results towards

the null, and mean that legacy effects may be larger than we estimated. The main limitation of our report is that because our findings are based on aggregate data, we are unable to assess the effects of whether or not an individual was treated with statins during the post-trial period, and for how long, as well as their cardiovascular risk factor levels and other potential confounders. For example although we found evidence of possible legacy effects in primary care, these are largely driven by WOSCOPs which was undertaken in all male participants. If there are sex-specific effects for legacy effects, it may be the fact that all participants in WOSCOPS were male, and not that they had no history of CVD, that is the more important determinant. Similarly, participants in WOSCOPS had the lowest percentage taking statins in the post trial period out of all the studies where this was measured (39% of active and 35% of placebo participants were taking statins at 5 years post-trial). This comparative absence of direct statin treatment effects in the post trial period may be the more important determinant.

We did not examine evidence of possible legacy effects on other outcomes such as non-fatal CVD, or for different post-trial follow-up times within each study, or for the same post-trial follow-up times between studies. We are aware of four other meta-analyses of data from long term follow-up after placebo controlled trials of lipid lowering treatment.(45-48) In three of these reports, the focus appears to have been on persistence of survival benefit, with comparison of event rates from time of randomisation, rather than post-trial legacy effect.(45, 47, 48) The other meta-analysis reported separate results for the post-trial period using data from earlier follow-up reports of six of our included trials.(46) That report found evidence of post-trial reduction in CVD mortality and all-cause mortality at two years, and evidence for a reduction in major coronary events at both two years and over the total post-trial periods. The authors did not explore possible causes of heterogeneity for the post-trial models such as whether the primary trial was for primary or secondary prevention.

Published trial evidence supports the hypothesis that lowering cholesterol with a statin drug reduces cardiovascular events.(49) Currently, the principle of using absolute risk to guide treatment decisions (as recommended by guidelines(50-53)) is that treatment is prioritised for those at highest short term risk, and people at low short term risk are not treated. Data on the efficacy and safety of statins has led to treatment thresholds being lowered: in the UK the threshold was lowered from >20% to >10% ten-year risk of CVD; in the US the threshold is 10% ten-year risk of CVD, with statins also recommended for selected patients with 7.5-10% ten-year risk.(53) However, as short term risk is largely driven by age, younger people are unlikely to qualify for statins even with these lowered thresholds. For example, a recent report found that in the absence of smoking or raised blood pressure, a ten-year risk of CVD above 5% was infrequent in women younger than 50 and men younger than 40 years resident in the US.(54)

Exploratory subgroup analysis in our study found evidence of possible legacy effects of statins following the primary prevention trials, which warrant further investigation. However, we note that the participants in WOSCOPS, ALLHAT and ASCOT-LLA had elevated levels of CVD risk factors (see table 1). Indeed, the majority of these people were likely to have been well above current treatment thresholds at the time of trial entry, and people with similar risk levels would now be recommended to start life-long lipid lowering treatment. For example, the proportion of people who had died of cardiovascular disease by the end of the trial in the placebo group after 3.3 years in ASCOT, 4.8 years in ALLHAT and 4.9 years in WOSCOPS was 3%, 11% and 2% respectively. Legacy effects in these settings serve to emphasise the benefits of starting long term primary prevention treatment early rather than

later among people at high short term risk. It does not provide evidence to support earlier treatment for people who have lower short term risk than current treatment thresholds.

Advocates of early intervention argue that people who are at risk of disease in the long term, but currently displaying no symptoms or signs of disease and at low calculated short term risk, should also be started on long term treatment at an early age.(5, 18) But deciding when, and if, to intervene in these people is much less straight forward. The legacy effect hypothesis for statins - that the earlier you start , the lower your risk of a CVD event in the long term- has not been tested directly in a RCT comparing statins commencement at an earlier versus later age, and such a trial is unlikely to eventuate. Indirect evidence from post-trial follow-up after the large statin trials is likely the next best way to investigate this.

CONCLUSION.

In this analysis of 8 long-term randomized trials, we found possible post-trial legacy effects of statins on CVD mortality and all-cause mortality for primary prevention. Although the post-trial relative benefits were clearly smaller than those observed within trials, the increasing risk with age may mean that the absolute benefits are similar. Analysis of individual patient data from follow-up studies after placebo similar RCTs in lower risk populations may provide more definitive evidence on whether early treatment of subclinical atherosclerosis is likely to be beneficial.

Authors contributions

Agnish Nayak acquired, analysed and interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Andrew Hayen undertook the main statistical analysis, interpreted the data, critically revised the manuscript for important intellectual content and approved the final version.

Lin Zhu acquired, analysed and interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Kevin McGeechan interpreted the data, critically revised the manuscript for important intellectual content and approved the final version.

Paul Glasziou interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Les Irwig obtained funding, interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Jenny Doust interpreted the data, critically revised the manuscript for important intellectual content and approved the final version

Gabriel Gregory interpreted the data, contributed to the statistical analysis, critically revised the manuscript for important intellectual content and approved the final version.

Katy Bell obtained funding, conceived the study and design, acquired, analysed and interpreted the data:, supervised the study, drafted the manuscript and revised for important

intellectual content and approved the final version. She had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Figures

Fig 1. Direct (within-trial) and legacy (post-trial) effects of statins on CVD mortality for 8 trials

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 2. Direct (within-trial) and legacy (post-trial) effects of statins on All-cause mortality for 8 trials.

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 3. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins on CVD mortality for 8 trials

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 4. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins on All-cause mortality for 8 trials.

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 5: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on CVD mortality for 4 trials

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 6: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on All-cause mortality for 4 trials

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

Fig 7: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on CVD mortality for 3 primary prevention trials

Note: Studies are ordered by duration of follow-up.

Fig 8: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on All-cause mortality for 3 primary prevention trials.

Note: Studies are ordered by duration of follow-up.

602 **Table 1. Characteristics of the 8 included studies**

Study	Target population	Dates of recruit-ment	Mean follow-up (years)	Statin	Number of participants	Proportion of women (%)	Mean age (range, years)	Diabetes (%)	History of CVD (%)	Duration of post-trial follow-up	Difference in proportion taking statins post-trial (%)
Primary Prevention/ Primary care population											
ALLHAT-LLT	Treated for high BP with high cholesterol	1994-1998	4.8	Pravastatin 40mg	10355	49	66 (55-?)	35	11	4	?
ASCOT-LLA	High BP and no history of CHD, with 3+ other CVD risk factors	1998-2000	3.2	Atorvostatin 10mg	10305	19	63 (40-79)	25	14	8.3	4
WOS-COPS	Men with high cholesterol and no history of myocardial infarction	1989-1991	4.8	Pravastatin 40mg	6595	0	55 (45-64)	1	8	15.1	4
Secondary Prevention/ Clinical population											

ALERT	Renal or combined renal and pancreas transplant recipients at high risk of CVD	1996-1997	5.1	Fluvastatin 40mg	2102	34	50 (30-75)	19	19	1.6	0
SSSS	History of angina or myocardial infarction	1988-1989	5.2	Simvastatin 20-40mg	4444	19	60+ (35-70)	5	100	5	4
PROSPER	≥70 years with history of CVD or at high risk of CVD	1997-1999	3.2	Pravastatin 40mg	5804	52	75 (70-82)	11	44	5.4	?
HPS	Coronary disease, other occlusive arterial disease, diabetes or treated for high BP	1994-1997	5.0	Simvastatin 40mg	20536	25	64 (40-80)	29	85	5.7	0
LIPID	Myocardial infarction or hospitalization for unstable angina	1990-1992	5.6	Pravastatin 40mg	9014	17	62 (31-75)	9	>99	10	1

603

604 **Notes**

605 1. CVD = Cardiovascular Disease

606 Order of trials within primary prevention and secondary prevention order is from shortest post-trial follow-up to longest.

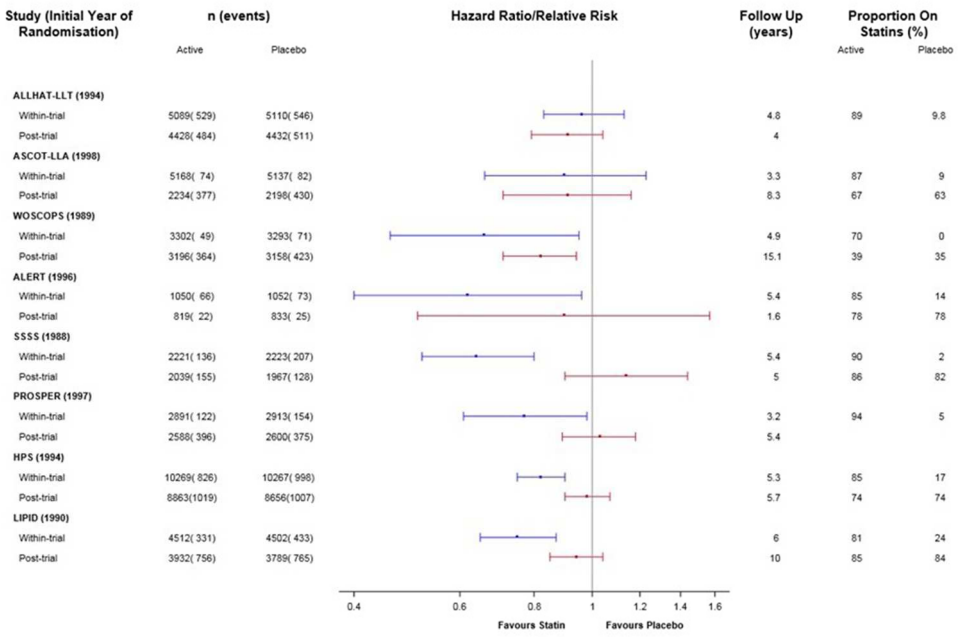

Fig 1. Direct (within-trial) and legacy (post-trial) effects of statins on CVD mortality. ┼ Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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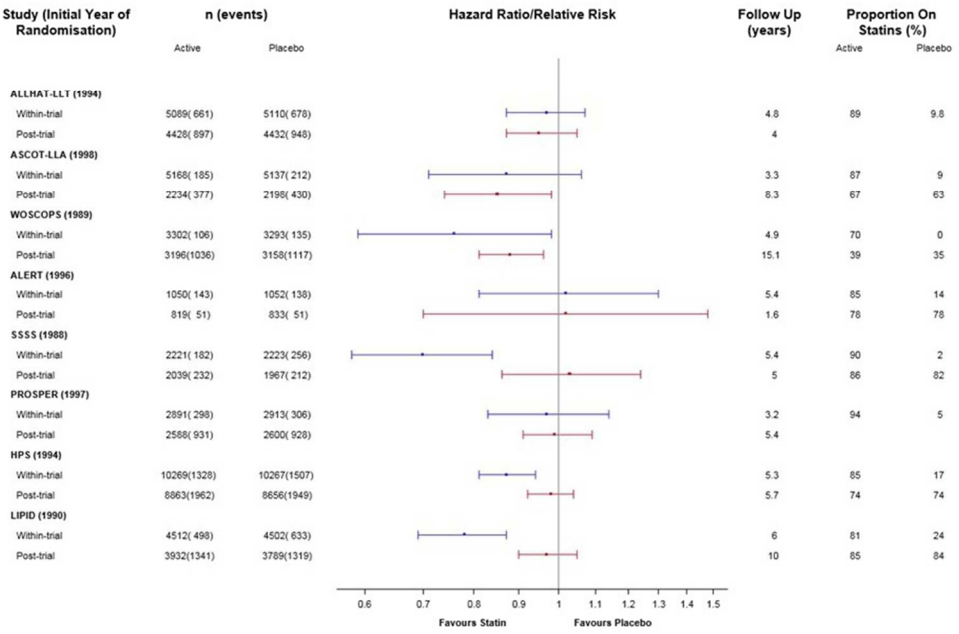

Fig 2. Direct (within-trial) and legacy (post-trial) effects of statins on All-cause mortality.

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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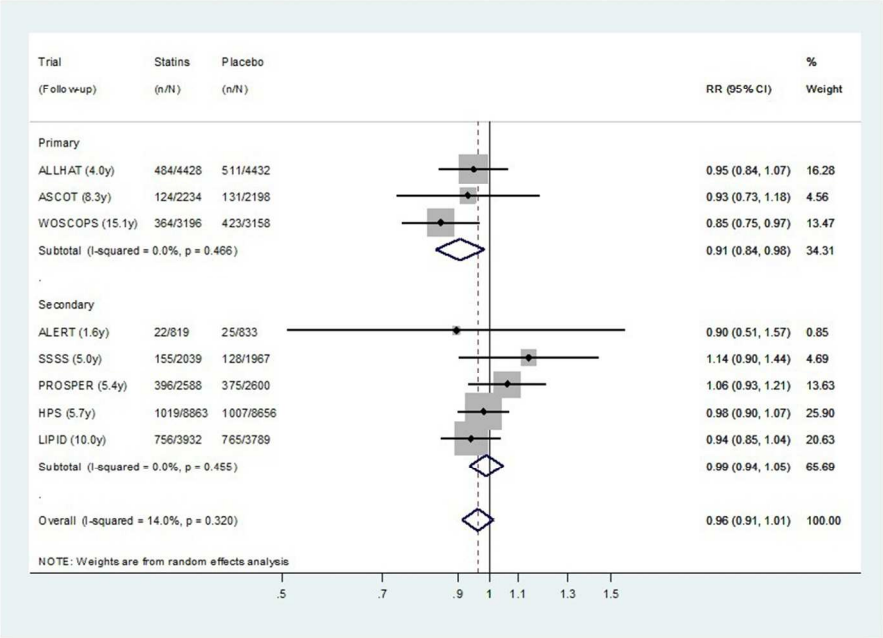

Fig 3. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins ⊦⊤ on CVD mortality.⊦⊤ Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.⊦⊤

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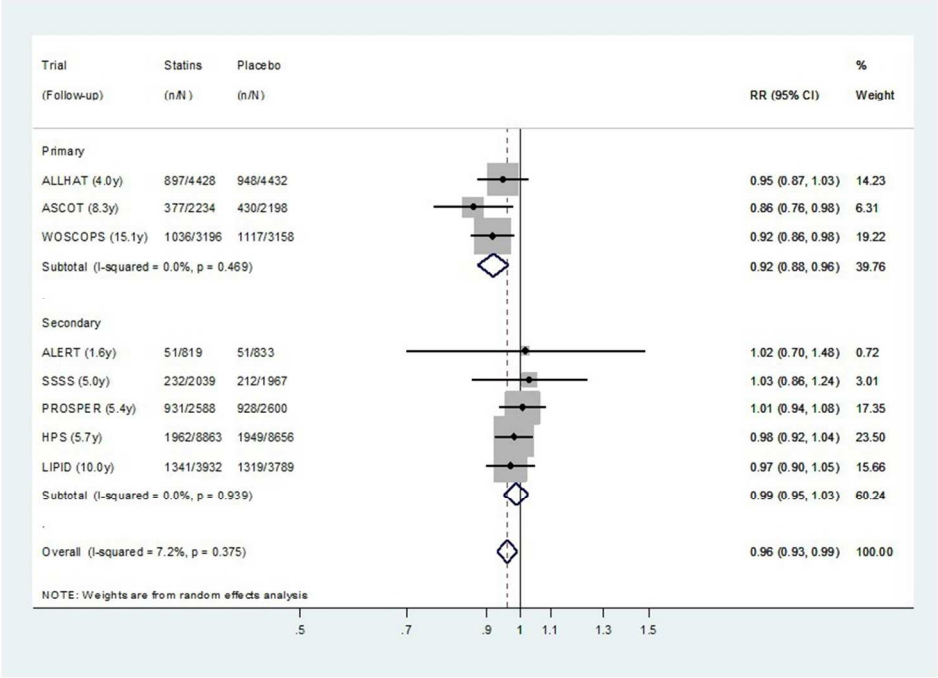

Fig 4. Random effects meta-analysis of relative risks for legacy (post-trial) effects of statins on All cause mortality.├ ┬ Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.├ ┬

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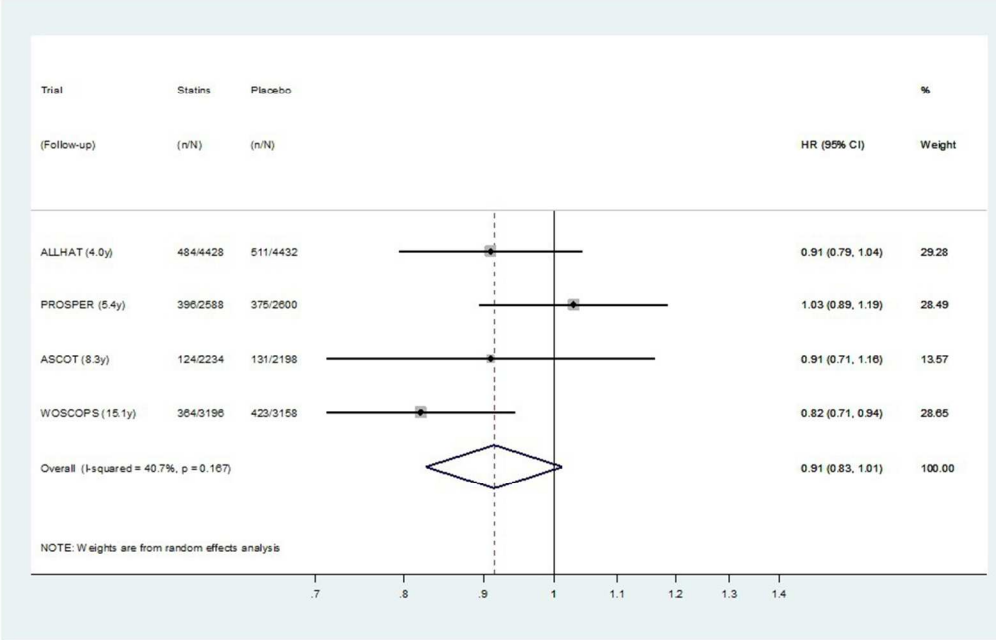

Fig 5: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins ‼ ┼ on CVD mortality for 4 trials. Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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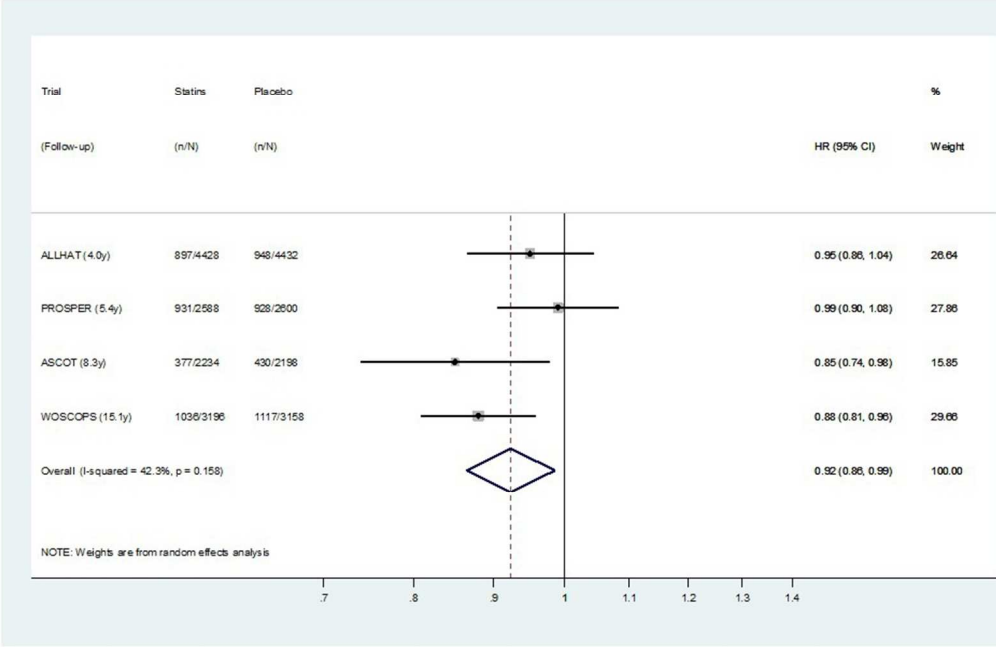

Fig 6: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on All-cause mortality for 4 trials.

Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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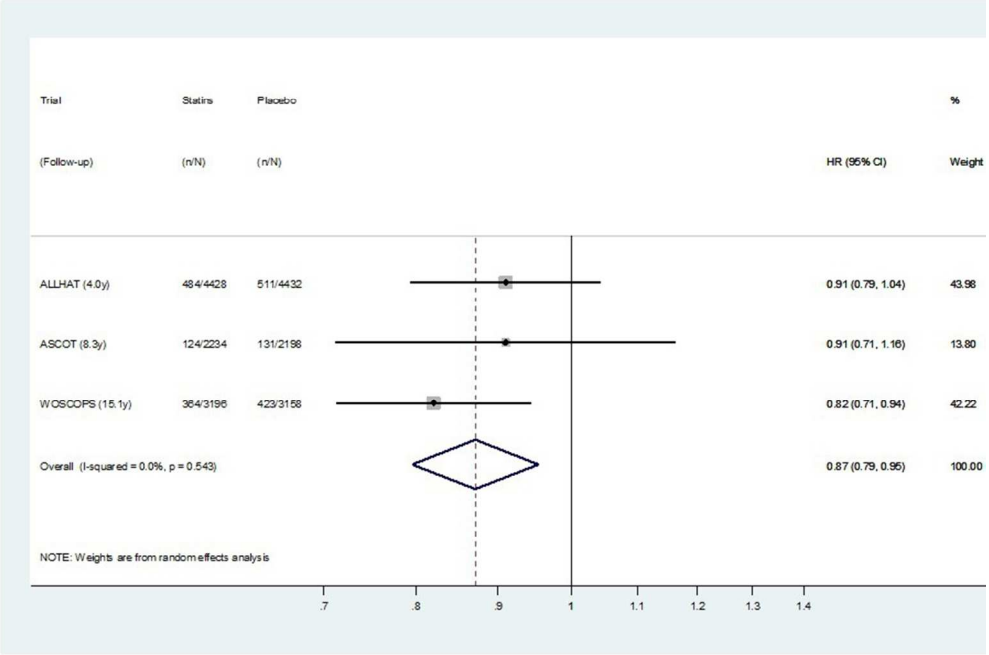

Fig 7. Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins on CVD mortality for 3 primary prevention trials.├ ┬ Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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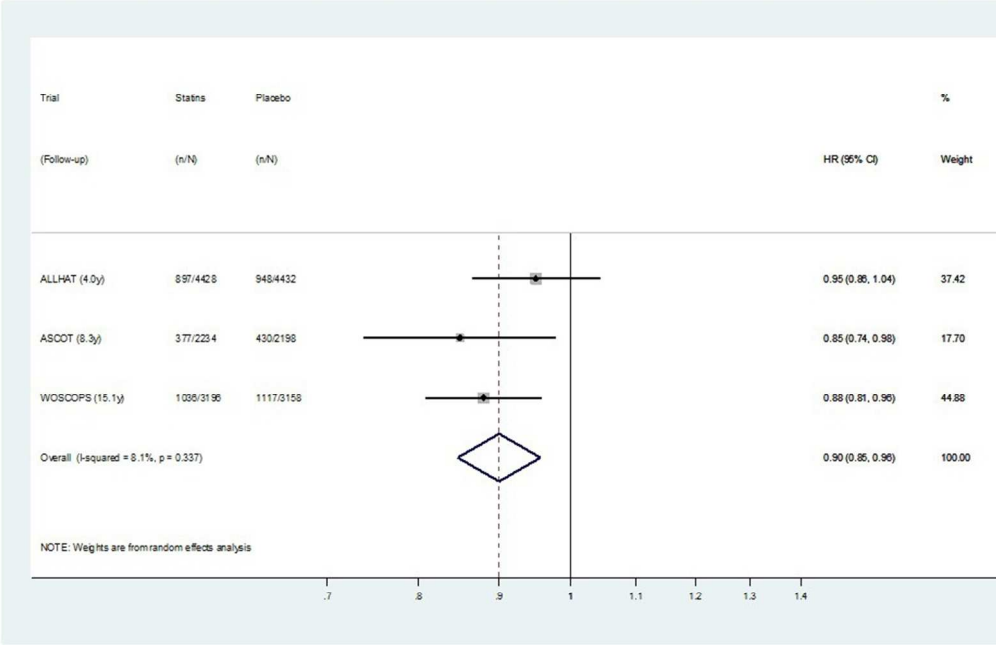

Fig 8: Random effects meta-analysis of Hazard Ratios for legacy (post-trial) effects of statins ‼ ┼ on All-cause mortality for 3 primary prevention trials. Note: Within primary and secondary prevention subgroups, studies are ordered by duration of follow-up.

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Simulation

We simulated outcomes for 4,000 people with equivalent pre-trial five-year CVD risk estimates for those who were randomized to have a statin or placebo. First, we set our simulation to include 2,000 people with baseline five-year risk of CVD mortality of 5% (high risk group) and 2,000 people with five-year risk of CV mortality of 1% (low risk group). Second, within the two risk groups we randomized individuals to statin or placebo at a ratio of 1:1. Third, we applied a relative risk reduction on CVD mortality of 0.80 for individuals randomized to statin for the five years of the trial period. Fourth, we applied 0.90 relative risk reduction for the scenario of a legacy effect (eFigure 1A & 1B) and applied no relative risk reduction for the scenario of no legacy effect (eFigure 1C & 1D). After the trial, all individuals were followed until they had an event, up to a further 20 years. For simplicity, we did not include any effects for aging in the model. The simulation was run 1000 times in R 3.3.1. Survival and hazard curves were generated by calculating the average results.

eFigure 1. Survival and Hazard curves using simulated data.

Fig 1A. Survival curves using simulated data where there is a legacy effect.

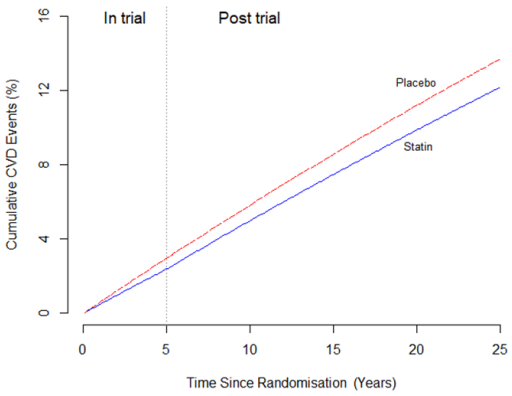


Fig 1B. Hazard curves using simulated data where there is a legacy effect.

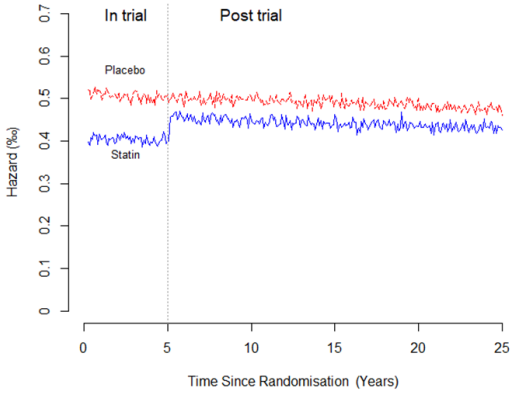


Fig 1C. Survival curves using simulated data where there is no legacy effect.

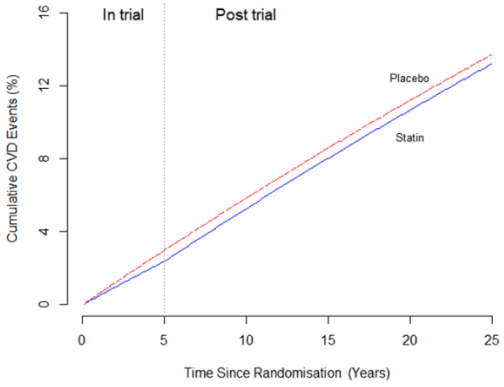
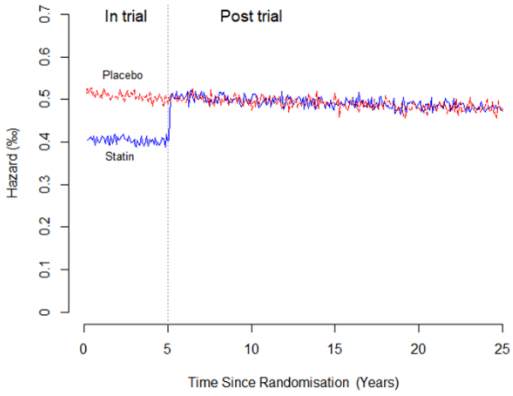


Fig 1D. Hazard curves using simulated data where there is no legacy effect.



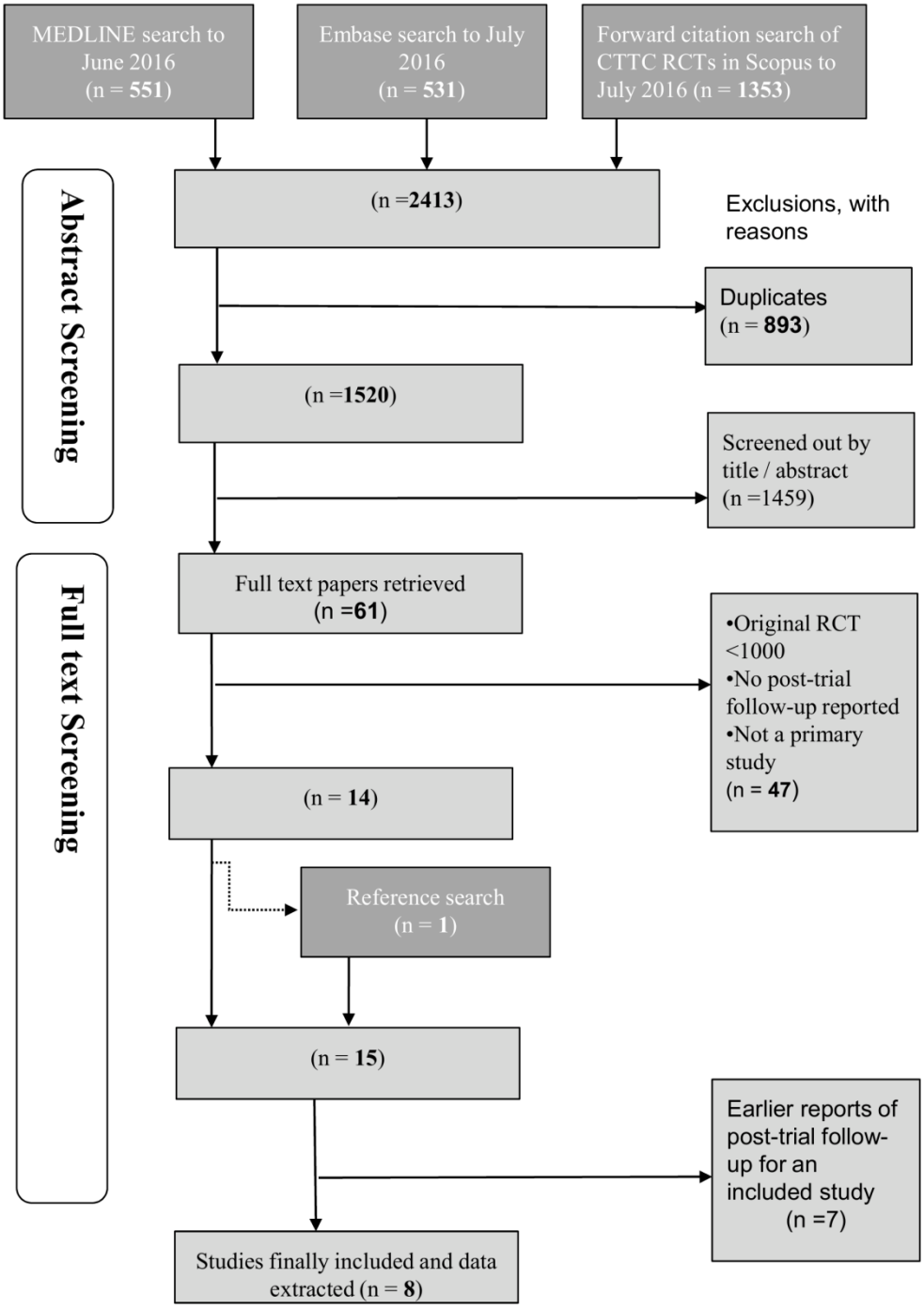
1A: Survival Curves, legacy effect; 1B: Hazard Curves, legacy effect; 1C: Survival Curves, no legacy effect; 1D: Hazard Curves, no legacy effect

During RCT period (5 years): Relative Risk Reduction for CVD mortality=0.80; during post-trial period (20 years): Relative Risk Reduction for CVD mortality =1 (i.e. no legacy effect).

Exaggeration of apparent legacy benefit is observed in the Survival Curves because of contribution of within-trial treatment effects on cummalitve incidence. Unbiased estimation

of post-trial legacy effects are shown in the Hazard Curves (note that these are curves of the instantaneous hazard at each time point, and are not curves of hazard ratios).

eFigure 2. Selection of primary studies



CTTC = Cholesterol Treatment Trialists' Collaboration

eTable 1 Effect of treatment allocation on All-cause mortality and CVD-mortality reported within trial period

Study	Difference in proportion taking statins within-trial (%)[1]	Allocated to statins			Allocated to placebo			Risk Estimates	
		N	All deaths	CVD deaths	N	All deaths	CVD deaths	All deaths	CVD deaths
ALLHAT-LLT	79	5089	661	529	5110	678	546	0.97 (0.87-1.07)[2]	0.96 (0.83-1.13)[2]
ASCOT-LLA	78	5168	460	154	5137	520	167	0.87 (0.71-1.06)[2]	0.90 (0.66-1.23)[2]
WOS-COPS	70	3302	106	49	3293	135	71	**0.76 (0.59-0.98)[2]**	**0.66 (0.46-0.95)[2]**
ALERT	71	1050	143	66	1052	138	73	1.02 (0.81-1.30)[3]	**0.62 (0.40-0.96)[3]**
SSSS	88	2221	182	136	2223	256	207	**0.70 (0.58-0.84)[3]**	**0.64 (0.52-0.80)[3]**
PROSPER	89	2891	298	122	2913	306	154	0.97 (0.83–1.14)[2]	**0.77 (0.61–0.98)[2]**
HPS	68	10269	1328	826	10267	1507	998	**0.87(0.81-0.94)[3]**	**0.82 (0.75-0.90)[3]**
LIPID	57	4512	498	331	4502	633	433	**0.77 (0.69-0.87)[3]**	**0.75 (0.65-0.87)[3]**

Notes

1. Difference in % taking statins = [% taking statins in group allocated to statin in trial - % taking statins in group allocated to placebo in trial]
2. Studies reporting Hazard Ratio
3. Studies reporting Relative Risk

4. Statistically significant results are **bolded**
5. CVD = Cardiovascular Disease
6. Order of trials within primary prevention and secondary prevention is from shortest post-trial follow-up to longest.

eTable 2 Effect of treatment allocation on All-cause mortality and CVD-mortality reported for post-trial period

Study	Average post-trial follow-up	Difference in proportion taking statins post-trial (%)[1]	Allocated to statins			Allocated to placebo			Risk Ratio	
			N[4]	All deaths	CVD deaths	N[4]	All deaths	CVD deaths	All deaths	CVD deaths
ALLHAT-LLT	4	?	4428	897	484	4432	948	511	0.91 (0.79–1.04)[2]	0.95 (0.87-1.05)[2]
ASCOT-LLA	8.3	4	2234	377	124	2198	430	131	**0.85 (0.74-0.98)**[2]	0.91 (0.71-1.16)[2]
WOS-COPS	15.1	4	3196	1036	364	3158	1117	423	**0.88 (0.81-0.96)**[2]	**0.82 (0.71-0.94)**[2]
ALERT	1.6	0	811	51	22	820	51	25	1.01 (0.69 - 1.47)[3]	0.89 (0.51 - 1.56)[3]
SSSS	5	4	2039	232	155	1967	212	128	1.03 (0.86-1.24)[3]	1.14 (0.90-1.44)[3]
PROSPER	5.4	?	2588	931	396	2600	928	375	0.99 (0.91-1.09)[2]	1.03 (0.89-1.18)[2]
HPS	5.7	0	8863	1962	1019	8656	1949	1007	0.98 (0.90-1.07)[3]	0.98 (0.92-1.04)[3]
LIPID	10	1	3932	1341	756	3789	1319	765	0.97 (0.90-1.05)[3]	0.94 (0.85-1.04)[3]

Notes

1. Difference in % taking statins = [% taking statins in group allocated to statin in trial - % taking statins in group allocated to placebo in trial]
2. Studies reporting Hazard Ratio
3. Studies reporting Relative Risk
4. Number alive and followed post-trial
5. Statistically significant results are **bolded**

6. CVD = Cardiovascular Disease
7. Order of trials within primary prevention and secondary prevention is from shortest post-trial follow-up to longest

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9 (Box 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9,15
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	eFigure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eTable 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-13 eTables 2-3 Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14 Figures 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-14 Figures 2A, 2B, 3C,3D
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	5

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