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ORIGINAL ARTICLE

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Postponement of cardiovascular outcomes by statin use: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Objective: To estimate the average outcome postponement (gain in days to an event) for cardiovascular outcomes in a meta-analysis of randomized, controlled statin trials, including any myocardial infarction, any stroke and cardiovascular death.

Design: Systematic review of large randomized, placebo-controlled trials of statin use, including a random-effects meta-analysis of all included trials.

Data sources: We searched MEDLINE (15 July 2019) and ClinicalTrials.gov (16 October 2019).

Eligibility criteria for selecting studies: Randomized, placebo-controlled trials of statin use that included at least 1000 participants. We identified 15 cardiovascular outcomes that were reported in more than 2 trials.

Results: We included 19 trials. The summary outcome postponements for the 15 cardiovascular outcomes varied between −1 and 38 days. For four major outcomes, the summary outcome postponement in days was as follows: cardiovascular mortality, 9.27 days (95% CI: 3.6 to 14.91; $I^2 = 72\%$; 9 trials) non-vascular and non-cardiovascular mortality, 1.5 days (95% CI: −2.2 to 5.3; $I^2 = 0\%$; 6 trials) any myocardial infarction 18.0 days (95% CI; 12.1 to 24.1; $I^2 = 92\%$; 15 trials); and any stroke, 6.1 days (95% CI; 2.86 to 9.39; $I^2 = 66\%$; 14 trials).

Conclusion: Statin treatment provided a small, average postponement of cardiovascular outcomes during trial duration.

KEYWORDS

cardiovascular endpoints, cholesterol, effect measures, meta-analysis, outcome postponement, statins

1 | INTRODUCTION

Although statins have been a subject of trials for over 30 years, controversies about their effect magnitude still exist, and different trials have demonstrated substantial variations in effect size.[1] The effect size of preventive interventions, including statins, is often expressed as the relative risk reduction or number needed to treat (NNT). However, some patients may find it difficult to understand such measures.[1-4] Outcome postponement, that is, the average gain in

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event-free time of the study endpoint in all treated, is an alternative way to illustrate the effect of practically any preventive interventions,[5,6] which has shown some promise in terms of patients' understanding.[2]

Our group found an all-cause mortality postponement with statin use of 12.6 days (95% CI; 7.1-18.0) during 5 years of trial duration.[7] The effect of statins may be larger on specific cardiovascular events, and since these drugs were designed to prevent progression of atherosclerosis, all-cause mortality might not be an entirely appropriate measure of their overall effect, especially as severe non-fatal cardiovascular outcomes would impact on patients' quality of life.[8]

The aim of this meta-analysis was to estimate the average outcome postponement on fatal and non-fatal cardiovascular outcomes in randomized studies comparing statins to placebo.

2 | METHODS

We systematically reviewed large placebo-controlled trials of statins, calculated the postponement of outcomes and subjected it to a meta-analysis.

2.1 | Data sources and searches

We searched MEDLINE (search index date: 15 July 2019) using the following MeSH terms: statins, placebo, and random*. We also searched ClinicalTrials.gov (search index date: 16 October 2019) using the following terms: "statins" AND "placebo" (interventional). We screened the reference lists of the included papers for relevant publications.

2.2 | Study selection

We included randomized trials of at least 1000 patients, in which a statin intervention (any drug) was compared with placebo, with a follow-up of minimum 2 years.

2.3 | Data extraction and quality assessment

Two authors (MRH and KGM) independently extracted trial characteristics and outcome data from each included trial published in a journal. Any discrepancies were resolved by consensus. The extracted trial characteristics included duration; whether it represented primary, secondary or mixed intervention; and baseline low-density lipoprotein (LDL) cholesterol level. We defined primary prevention trials as trials in which no patients had manifest cardiovascular disease at baseline, secondary prevention trials as those in which all patients had cardiovascular disease, and mixed prevention trials as trials including patients both with and without cardiovascular disease. Two physicians independently performed trial classification. The effect data included hazard ratio (HR), or relative risk (RR), and 95% confidence interval (CI), and the event rate or cumulative events in the placebo group. For trials that reported relative risk (n = 8) instead of hazard ratio as the outcome measure, we used relative risk as a proxy for hazard ratio. These measures are very similar when the cumulative risk is low.[9] We used the 5-year standardized outcome postponements as input to reduce the influence of trial duration on outcome postponement and thereby to reduce the level of heterogeneity as shown in Hansen et al.[7]

Bias of the individual trials was assessed, and outcomes were grouped after type, using Cochrane's risk of bias tool.[10] If the published papers did not contain the essential parameters for our model, for example, mean trial follow-up, we contacted the authors. Five groups provided additional information. We followed PRISMA guidelines for systematic literature review and meta-analysis.[11]

2.4 | Data synthesis and analysis: postponement of outcomes in single trials

We calculated postponement of outcomes in each trial using two different methods, a mathematical modelling of the area between survival curves and a pixel counting of the area. We used linear regression to compare model-derived estimates with the corresponding estimates derived by pixel counting. Details of the two methods have been presented previously.[7] A description is given in Appendices A, B and C in the supplementary file.

2.5 | Data synthesis and analysis: meta-analysis

We performed meta-analyses on postponement of cardiovascular events using inverse variance weighting and random-effects models (Stata 15, Stata Corp, Texas, USA). We used the 5-year standardized outcome postponements as input. Finally, to assist in the interpretation of the postponement meta-analysis, we performed a HR-based meta-analysis of each cardiovascular event.

In order to account for heterogeneity by trial characteristics, we subgrouped according to high vs low overall risk of bias. In addition, we analysed trials according to the purpose of prevention, whether it be primary, secondary or mixed.

2.6 | Cardiovascular outcomes

We selected categories of cardiovascular outcomes that had been investigated in three trials or more. These included cardiac death, cardiovascular death, death from coronary heart disease, any myocardial infarction, non-fatal myocardial

infarction, any cardiovascular event, any coronary event, unstable angina, coronary revascularization, non-fatal stroke, fatal stroke, any stroke, death from non-vascular and non-cardiovascular causes, hospitalization for unstable angina and hospitalization for heart failure.

We categorized outcomes as "coronary revascularization" if reported as follows: coronary revascularization, revascularization procedures, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), and PCI or CABG. We categorized outcomes as "any myocardial infarction" if reported as follows: any myocardial infarction and death from CHD or non-fatal myocardial infarction. We categorized outcomes as "non-cardiovascular death" if reported as follows: death from non-cardiovascular causes and death from non-vascular causes. We categorized outcomes as "any stroke" if reported as follows: any stroke, fatal stroke and non-fatal cerebrovascular events. Outcomes were combined in this way if they, by clinical reasoning, were thought to have large overlap.

The systematic review was registered in PROSPERO [CRD42016037507].

2.7 | Patient involvement

Patients were not involved in the planning or conduct of the study.

3 | RESULTS

We identified 120 potentially eligible trials of which 101 were excluded (Figure 1), leaving 19 trials that met our inclusion criteria. The basic characteristics of the trials are reported in Table 1. Of the 19 trials, four (21%) were for primary prevention, six (32%) were for secondary prevention, and nine (47%) were for mixed prevention.

Table 2 shows the results of the meta-analyses grouped by cardiovascular outcome. The modelled outcome postponement for the four major outcomes was (standardized to 5 years of trial duration), cardiovascular mortality 9.3(95% CI: 3.6 to 14.9; $I^2 = 72\%$; trials), non-vascular and non-cardiovascular mortality 1.5 days (95% CI: −2.2 to 5.3; $I^2 = 0\%$; 6 trials), any myocardial infarction 18.0 days (95% CI; 12.1 to 24.1; $I^2 = 92\%$; 15 trials) and any stroke 6.1 days (95% CI: 2.9 to 9.4; 14 trials). Forest plots for these estimates are presented in Figures 2-5, and the remaining forest plots included in our analysis are shown as Figures S3-S13.

Table 3 presents the results of modelled outcome postponement from the individual trials (standardized to a 5-year trial duration). The largest gain in outcome postponement was found for any cardiovascular event in the SPARCL trial, that is, 83 days (95% CI; 54 to 109). The least favourable outcome was found in the 4D trial for any stroke, −25.0 (−72.0 to 7.7). Figure S1 presents the non-standardized outcome postponements, and corresponding results obtained by the use of the Pixel Counting Method are shown in Figure S2. We found a strong agreement between modelled outcome and corresponding estimates from pixel counting, with a slope of 0.95 with linear regression.

When subgrouping on trial duration, the postponement was substantially larger among trials with a duration above ≥ 5 years than below < 5 years, 18.6 days vs 6.3 days, respectively.

All included trials were very large, with accessible protocols, concealed allocation and blinding. All trials had a low overall risk of bias as evaluated by the Cochrane risk of bias tool. No trials were assessed as high risk of attrition bias; only two trials were assessed as unclear, the rest were assessed as low risk of bias.

Treatment switches are a concern as some trials described varying percentages of patients (range, 4.8%-25.4%) assigned to the placebo group switching to statin treatment, or were assigned to the statin group, but stopped their treatment. We analysed treatment switches with respect to any myocardial infarction. Outcome postponement was 16.3 days (CI, 10.0-22.7) in the nine trials with high cumulative incidence (>4%) of treatment switches, 73.4 days (CI, 54.1-92.7) in the single trial with a low degree of switching, and 16.9 days (PI, 6.5-27.4) in the 5 trials with an unclear degree of switching.

All trials included in this meta-analysis were analysed using the intention-to-treat principle which protects against bias due to difference in prognosis between patients switching treatment groups and not, but the procedure is conservative and may bias the effect estimate towards the null value. Some of the included trials reported large proportions of patients switching from the placebo group to the statin group,

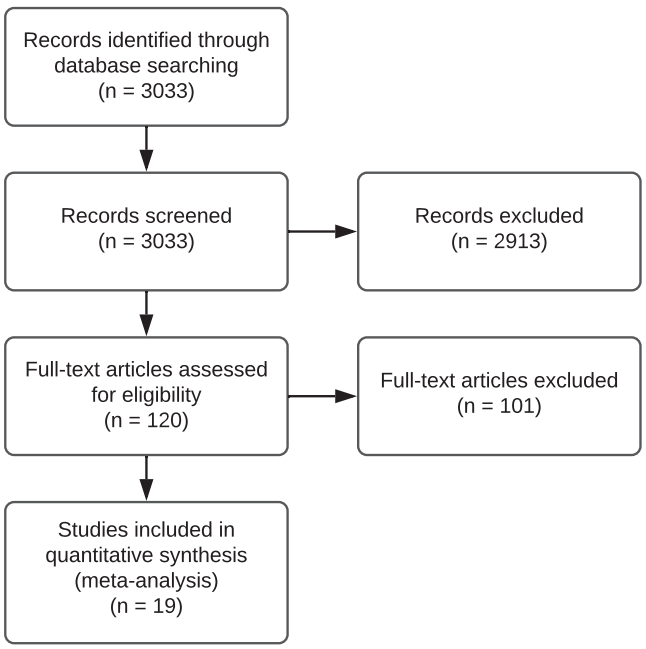

FIGURE 1 Flow chart of included studies

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TABLE 1 Characteristics of the included trials

Trial name	Statin and daily dose	Type of prevention	Number of patients		Trial duration (y)	Baseline LDL-C (mmol/L)[8,18]	LDL-C difference at 1 y , compared to baseline (mmol/L)§ [8,18]
			Statin	Placebo			
ASCOT-LLA[19]	Atorvastatin (10 mg)	Mixed	5168	5137	3.5	3.44	−1.07
[a]CARDS[20]	Atorvastatin (10 mg)	Primary	1428	1410	4.75	3.03	−1.14
ASPEN[18]	Atorvastatin (10 mg)	Mixed	1211	1199	4.25	2.93	−0.99
4D[21]	Atorvastatin (20 mg)	Mixed	619	636	6	3.25	−0.89
SPARCL[22]	Atorvastatin (80 mg)	Secondary	2365	2366	6	3.44	NA
[a]WOSCOPS[23]	Pravastatin (40 mg)	Mixed	3302	3293	6	4.96	−1.07
[a]CARE[24]	Pravastatin (40 mg)	Secondary	2081	2078	5.5	3.58	−1.03
[a]LIPID[25]	Pravastatin (40 mg)	Secondary	4512	4502	6.63	3.88	−1.03
PROSPER[26]	Pravastatin (40 mg)	Mixed	2891	2913	3.7	3.79	−1.04
CORONA[27]	Rosuvastatin (10 mg)	Secondary	2497	2514	3	NA	NA
GISSI-HF[28]	Rosuvastatin (10 mg)	Mixed	2285	2289	4.5	3.06	−0.92
AURORA[29]	Rosuvastatin (10 mg)	Mixed	1389	1384	5	2.58	−0.99
JUPITER[30]	Rosuvastatin (20 mg)	Primary	8901	8901	4.5	2.7	−1.09
4S[31]	Simvastatin (10-40 mg)	Secondary	2221	2223	5.8	4.88	−1.77
[a]HPS[32]	Simvastatin (40 mg)	Mixed	10 269	10 267	6	3.38	−1.29
[a]ALERT[33]	Fluvastatin (40 mg)	Mixed	1050	1052	6	4.14	−0.84
[a]LIPS[34]	Fluvastatin (80 mg)	Secondary	844	833	4	3.42	−0.92
[a]AFCAPS[35]	Lovastatin (20-40 mg)	Primary	3304	3301	6	3.89	−0.94
[a]HOPE[36]	Rosuvastatin (10 mg)	Primary	6361	6344	7.46	3.31	−1.02

Note: All were randomized trials comparing a statin vs placebo, ≥1000 patients, with a follow-up of minimum 2 y.

Abbreviations: LDL-C, low-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NA, not available.

[§]The LDL-C is the difference between the statin group and the placebo group at 1 y.

[a]RR used instead of HR.

TABLE 2 Meta-analyses of postponement of 15 different cardiovascular outcomes

Subgroup	Number of trials	Non-standardized outcome postponement, days (95% CI)	I^2 (%)	Outcome postponement standardized to 5 y, days (95% CI)	I^2 (%)	HR-based meta-analysis, HR (95% CI)	I^2 (%)
Cardiac death	4	11.6 (−0.8 to 24.0)	65	12.2 (−0.5 to 25.0)	71	0.77 (0.62 to 0.95)	16
Cardiovascular mortality	9	11.9 (4.0 to 19.7)	80	9.3 (3.6 to 14.9)	72	0.85 (0.77 to 0.95)	64
Death from CHD	4	11.9 (5.1 to 18.7)	56	10.1 (5.0 to 5.2)	40	0.76 (0.68 to 0.85)	0
Any myocardial infarction	15	19.8 (13.7 to 25.8)	90	18.0 (12.1 to 24.0)	92	0.71 (0.66, 0.76)	38
Non-fatal myocardial infarction	10	24.6 (14.6 to 34.7)	90	19.9 (13.5 to 26.4)	82	0.69 (0.61 to 0.78)	65
Any cardiovascular event	4	39.2 (16.8 to 61.5)	84	38.0 (15.5 to 60.5)	84	0.77 (0.70 to 0.84)	26
Any coronary event	5	20.7 (8.7 to 32.64)	82	21.7 (14.3 to 29.2)	46	0.73 (0.61 to 0.87)	75
Unstable angina	4	4.4 (−1.0 to 9.8)	71	3.1 (−0.7 to 6.8)	63	0.84 (0.74 to 0.95)	0
Coronary revascularization	12	21.9 (13.3 to 30.4)	91	16.5 (9.6 to 23.4)	92	0.72 (0.66, 0.78)	43
Non-fatal stroke	5	5.1 (2.4 to 7.7)	1	6.6 (3.5 to 9.8)	0	0.89 (0.73 to 1.10)	53
Fatal stroke	3	1.4 (−10.7 to 13.4)	81	−0.6 (−11.8 to 10.6)	75	1.19 (0.52 to 2.71)	82
Any stroke	14	6.6 (3.1 to 10.0)	63	6.1 (2.9 to 9.4)	66	0.85 (0.76 to 0.96)	62
Death from non-CV causes.	6	1.2 (−3.6 to 5.9)	0	1.5 (−2.2 to 5.3)	0	0.97 (0.90 to 1.05)	0
Hospitalizations for unstable angina	3	5.3 (−2.4 to 13.0)	76	8.1 (−2.8 to 19.1)	71	0.88 (0.81 to 0.95)	0
Hospitalizations for heart failure	3	5.0 (−1.5 to 11.6)	0	8.3 (−3.4 to 20.1)	0	0.94 (0.87 to 1.01)	0

Abbreviations: 95% CI, 95% confidence interval; CHD, coronary heart disease; CV, cardiovascular; HR, hazard ratio.

or patients who were in the statin group, but ceased treatment (range, 4.8%-32%). For any myocardial infarction, outcome postponement was 16.3 days (95% CI; 100-22.7) in the nine trials with high cumulative incidence (>4%) of treatment switches, 55.4 days (95% CI; 40.9-70.0) in the single trial with a low degree of switching and 13.4 days (95% CI; 6.5-20.3) in the five trials with an unclear degree of switching.

4 | DISCUSSION

In this meta-analysis of 19 large randomized, controlled trials, we demonstrated that statin treatment resulted in small average outcome postponement for cardiovascular endpoints. Since statins primarily prevent progression of atherosclerosis,[8] we anticipated that the postponement for strictly cardiovascular outcomes would be larger than for all-cause death. In general, our findings were consistent with this model of understanding; postponements were slightly more pronounced for cardiac outcomes than for all-cause mortality, and strictly non-vascular outcomes were not postponed at all. As expected, the effect of statin therapy on stroke prevention was modest. For four major outcomes, that is, cardiovascular mortality, non-cardiovascular mortality, any myocardial infarction and any stroke, the summary outcome postponement was 9.3, 1.5, 18.0 and 6.1 days, respectively, when standardized to 5 years of trial duration.

When we stratified according to prevention type, we found the largest postponement in the secondary prevention group, which was expected. Our HR-based meta-analysis showed particularly large relative risk reductions for cardiovascular mortality and non-fatal myocardial infarction. Although generated from the same source data, the magnitude of the relative risk reductions and the corresponding outcome postponement values may seem contradictory. A key factor in understanding this apparent discrepancy is that outcomes rates are generally low in these trials. Consequently, a large relative risk reduction that represents a modest absolute risk reduction translates into a small outcome postponement.

Outcome postponement has been widely appraised as a tool for conveying the effect of preventive treatment to patients. It appears to be superior to NNT in some respects.[2] Patients show much more responsiveness when being informed by the use of the outcome postponement than by other measures, that is, their preferences with respect to accepting or rejecting a proposed drug intervention changes when they are presented with different values for the postponement. For NNT, a similar proportion of patients accepts treatment, whether they are presented with values between 10 and 400.[2] It has been demonstrated that patients are more responsive to information conveyed through outcome postponement, that is, their chance of accepting a treatment increases when they are presented with higher values of outcome postponement. On the other hand, even extreme differences in the presented values of NNT do not lead to greater or lower rates of treatment acceptance.[2] A recent study randomized practices to use either absolute risk reduction or outcome postponement, when informing patients about the effect of statins. The study

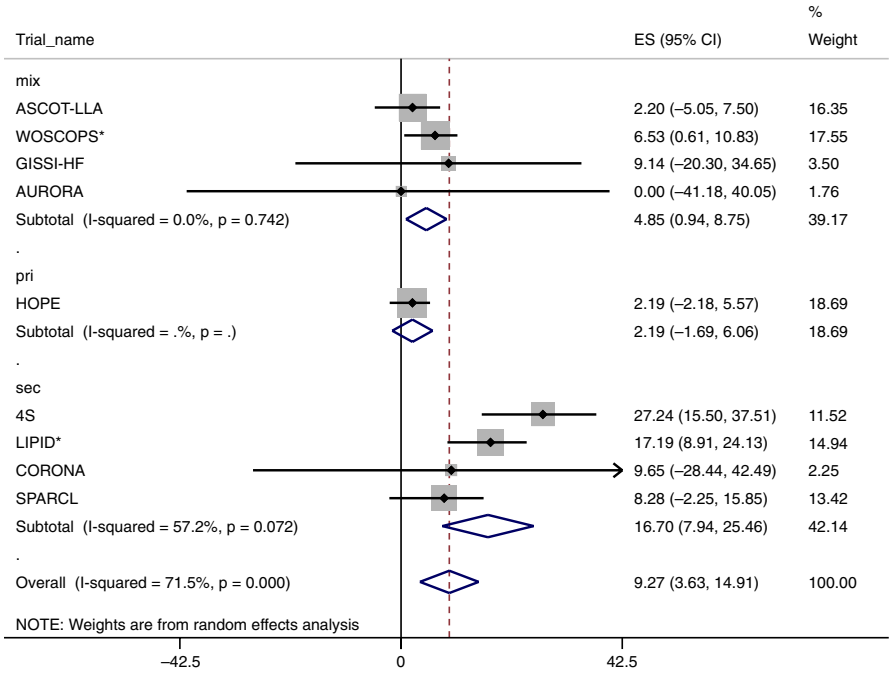

FIGURE 2 Forest plots of postponement of cardiovascular mortality standardized to 5 y of trial duration, grouped according to prevention type. Mix, mixed prevention; Sec, secondary prevention

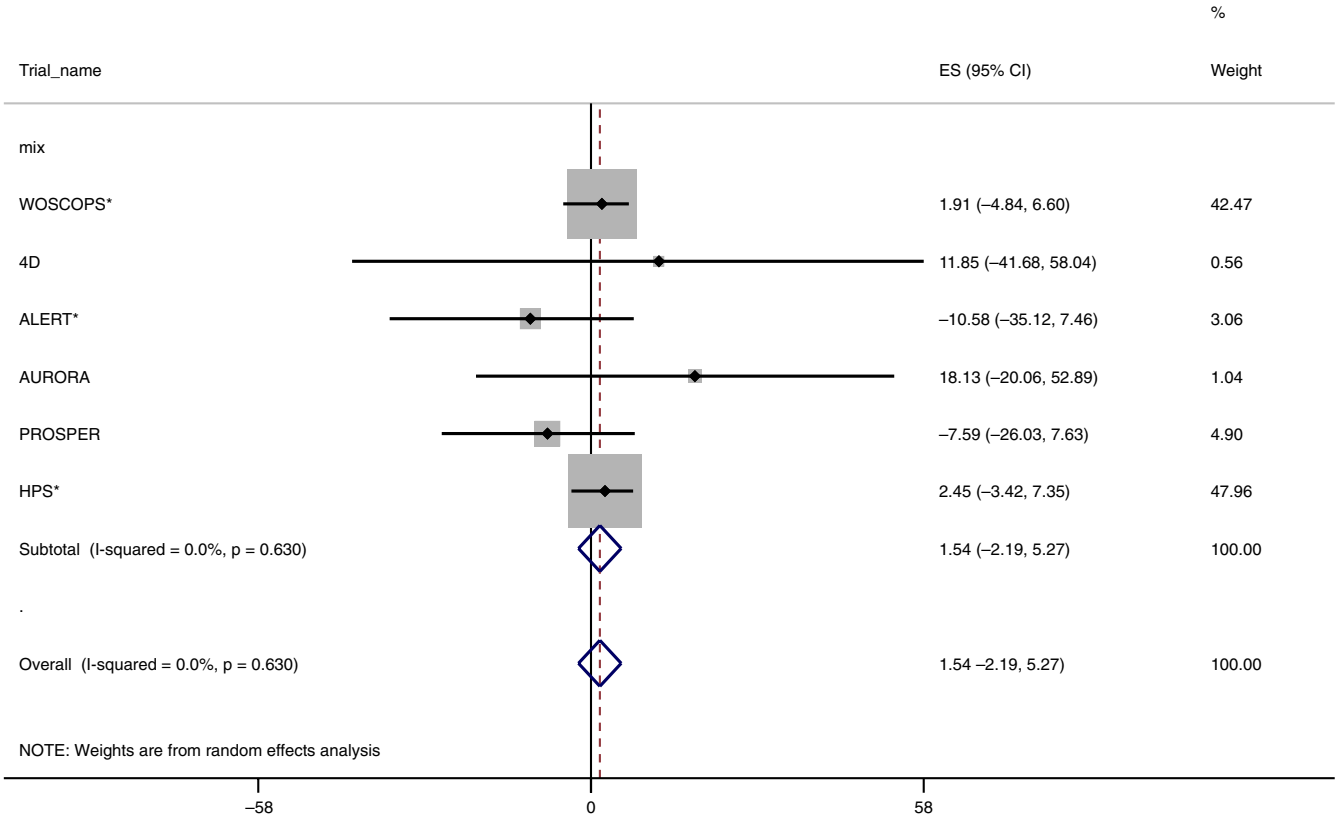

FIGURE 3 Forest plots of postponement of death from non-vascular and non-cardiovascular mortality standardized to 5 y of trial duration, grouped according to prevention type. Mix, mixed prevention. *RR used instead of HR

found a markedly lower proportion of patients redeeming their prescriptions if outcome postponement was used, even though the presented values reflected the same effect magnitude.[12] A survey examined which threshold of absolute risk reduction and outcome postponement that would be required for the patients to accept preventive drugs. The lowest effect for patients to accept a hypothetical cholesterol-lowering drug varied, depending on their risk profile, from 20% to 30% in absolute risk reduction, and from 12 to 18 months on outcome postponement.[13] Few, if any, preventive drugs

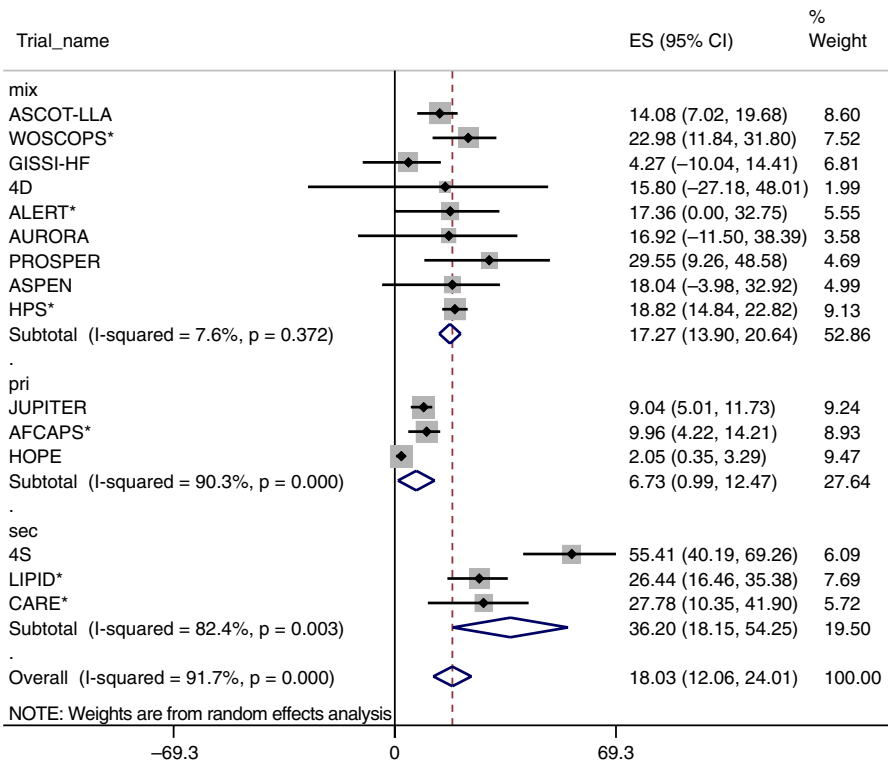

FIGURE 4 Forest plots of postponement of any myocardial infarction, standardized to 5 y of trial duration, grouped according to prevention type. Mix, mixed prevention; Pri, Primary prevention; Sec, secondary prevention. *RR used instead of HR

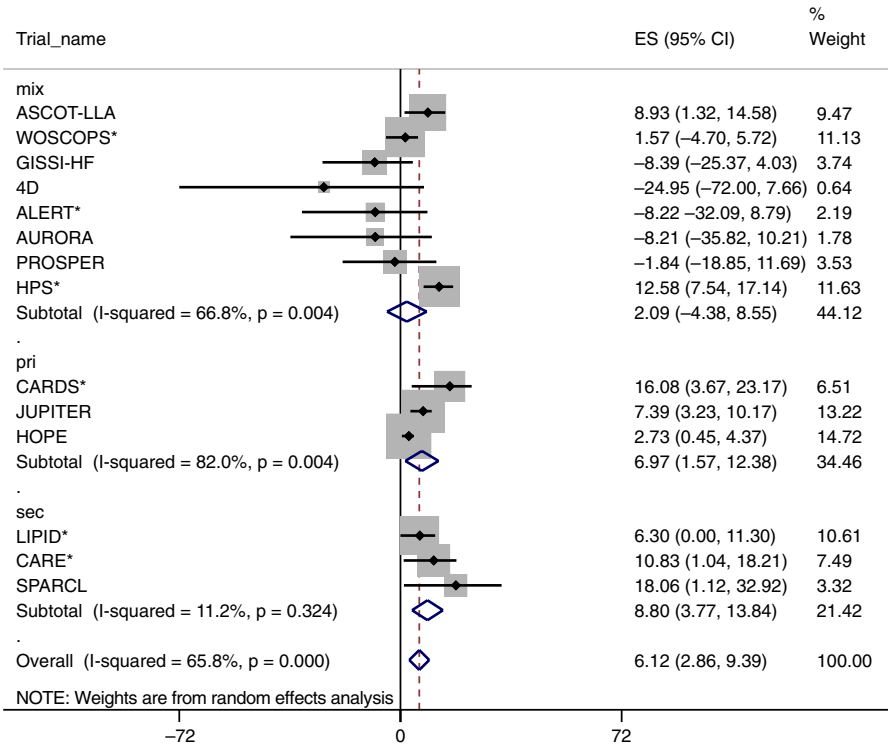

FIGURE 5 Forest plots of postponement of any stroke, standardized to 5 y of trial duration, grouped according to prevention type. Mix, mixed prevention; Pri, Primary prevention; Sec, secondary prevention. *RR used instead of HR

can demonstrate such effects. Thus, there might be a gap between reality and patient expectations pertaining to the effect of preventive drugs.

The main limitation of using outcome postponement is the inability of the measure to capture the benefit of continued treatment in the decades after trial termination, although this is a limitation that applies to all effect measures currently used.[7] The outcome postponement will continue to grow after trial termination as long as the survival curves are separated. Unfortunately, estimating the effect of continued statin treatment is difficult and depends heavily on untestable assumptions. For instance, some attempts to estimate the outcome postponement after trial termination assumed that the HR achieved during the trial will remain applicable

TABLE 3 Results of outcome postponement calculations from the mathematical model standardized to 5 y of trial duration, with 95% confidence interval

Trial name	Cardiac death	Cardiovascular death	Death from CHD	Any myocardial infarction	Non-fatal myocardial infarction	Any cardiovascular event	Any coronary event	Unstable angina
Panel (A)								
ASCOT-LLA	-	2.2 (−5.1 to 7.5)	-	14.1 (7.0 to 19.7)	-	-	19.3 (9.3 to 27.3)	8.0 (−34.3 to 31.5)
CARDS[a]	-	-	-	-	-	47.9 (22.2 to 67.8)	23.3 (5.8 to 35.8)	-
ASPEN	-	-	-	18.0 (−4.0 to 32.9)	-	-	-	-
4D	43.6 (−6.7 to 83.9)	-	-	15.8 (−27.2 to 48.0)	15.8 (−27.2 to 48.0)	-	-	-
SPARCL	0.0 (−8.5 to 5.5)	8.3 (−2.2 to 15.9)	-	-	15.5 (8.2 to 20.7)	59.4 (38.5 to 78.2)	32.2 (20.6 to 41.6)	-
WOSCOPS[a]	-	6.5 (0.6 - 10.8)	5.6 (0.2 to 9.4)	23.0 (11.8 to 31.8)	18.0 (8.0 to 26.7)	-	-	-
CARE[a]	-	-	10.5 (−2.6 to 20.6)	27.8 (10.3 to 41.9)	22.7 (5.9 to 35.7)	-	-	19.1 (−1.5 to 37.0)
LIPID[a]	-	17.2 (8.9 to 24.1)	14.3 (7.1 to 20.9)	26.4 (16.5 to 35.4)	-	-	-	-
PROSPER	-	-	13.8 (0.6 to 24.2)	29.5 (9.3 to 48.6)	16.0 (−3.4 to 32.2)	32.4 (6.4 to 54.5)	-	-
CORONA	-	9.7 (−28.4 to 42.5)	-	-	-	-	26.7 (−13.1 to 61.0)	-
GISSI-HF	-	9.1 (−20.3 to 34.7)	-	4.3 (−10.0 to 14.4)	-	-	-	-
AURORA	-	0.0 (−41.2 to 40.0)	-	16.9 (−11.5 to 38.4)	16.9 (−11.5 to 38.4)	-	-	-
JUPITER	-	-	-	9.0 (5.0 to 11.7)	9.7 (6.3 to 11.7)	-	-	-
4S	-	27.2 (15.5 to 37.5)	-	55.4 (40.2 to 69.3)	55.4 (40.2 to 69.3)	-	-	-
HPS[a]	-	-	-	18.8 (14.8 to 22.8)	18.8 (14.8 to 22.8)	-	-	-
ALERT[a]	17.0 (1.8 to 26.9)	-	-	17.4 (0.0 to 32.7)	17.4 (0.0 to 32.7)	-	-	-
LIPS[a]	15.6 (−1.6 to 24.2)	-	-	-	-	-	-	-
AFCAPS[a]	-	-	-	10.0 (4.2 to 14.2)	-	16.2 (5.8 to 24.8)	13.8 (4.4 to 21.6)	7.3 (1.1 to 11.7)
HOPE	-	2.2 (−2.2 to 5.6)	-	2.1 (0.4 to 3.3)	-	-	-	1.0 (−1.8 to 2.9)

(Continues)

TABLE 3 (Continued)

Trial name	Coronary revascularization	Non-fatal stroke	Fatal stroke	Any stroke	Death from non-CV cause	Hospitalizations for unstable angina	Hospitalizations for heart failure
Panel (B)							
ASCOT-LLA	-	-	-	8.9 (1.3 to 14.6)	-	-	-
CARDS[a]	6.6 (−3.4 to 12.5)	-	-	16.1 (3.7 to 23.2)	-	-	-
ASPEN	-	-	-	-	-	-	-
4D	-	−2.3 (−38.4 to 20.5)	−24.0 (−67.2 to −1.2)	−25.0 (−72.0 to 7.7)	11.9 (−41.7 to 58.0)	-	-
SPARCL	27.9 (17.3 to 35.4)	13.3 (−3.0 to 27.8)	6.9 (0.8 to 10.4)	18.1 (1.1 to 32.9)	-	-	-
WOSCOPS[a]	8.3 (2.5 to 12.5)	-	-	1.6 (−4.7 to 5.7)	1.9 (−4.8 to 6.6)	-	-
CARE[a]	43.2 (23.8 to 59.6)	-	-	10.8 (1.0 to 18.2)	-	-	-
LIPID[a]	21.8 (10.9 to 30.6)	-	-	6.3 (0.0 to 11.3)	-	19.5 (6.5 to 31.0)	-
PROSPER	4.2 (−6.0 to 10.7)	1.1 (−14.4 to 13.5)	−3.9 (−14.1 to 1.4)	−1.8 (−18.8 to 11.7)	−7.6 (−26.0 to 7.6)	-	5.2 (−10.3 to 16.7)
CORONA	-	-	-	-	-	4.7 (−14.1 to 18.0)	34.5 (−7.5 to 70.2)
GISSI-HF	-	-	-	−8.4 (−25.4 to 4.0)	-	-	8.4 (−24.8 to 36.8)
AURORA	2.9 (−33.1 to 32.5)	-	-	−8.2 (−35.8 to 10.2)	18.1 (−20.1 to 52.9)	-	-
JUPITER	-	6.7 (2.8 to 9.4)	-	7.4 (3.2 to 10.2)	-	2.6 (−0.6 to 4.3)	-
4S	51.2 (35.7 to 63.9)	-	-	-	-	-	-
HPS[a]	18.6 (13.6 to 23.6)	-	-	12.6 (7.5 to 17.1)	2.4 (−3.4 to 7.3)	-	-
ALERT[a]	6.2 (−9.2 to 15.8)	-	-	−8.2 (−32.1 to 8.8)	−10.6 (−35.1 to 7.5)	-	-
LIPS[a]	-	-	-	-	-	-	-
AFCAPS[a]	13.4 (6.1 to 19.6)	-	-	-	-	-	-
HOPE	2.3 (0.4 to 3.8)	-	-	2.7 (0.5 to 4.4)	-	-	-

Abbreviations: CHD, coronary heart disease; CV, cardiovascular.

[a]RR used instead of HR.

after trial termination, and that patients will continue statin treatment with near-perfect adherence, something that has proven unrealistic in most drug utilizations studies.[14,15]

As an indicator of what a realistic outcome postponement for all-cause mortality could be for long-term statin treatment, we used the long-term follow-up on the WOSCOPS trial by Ford et al,[16] demonstrating a hazard ratio for all-cause mortality of 0.87 (CI 95% 0.80-0.94). We calculated outcome postponement for the 20-year follow-up by using variables available in the paper, estimating an outcome postponement of 152 days (95% CI; 70-236 days) for 20 years. The patients were kept on placebo for the duration of the trial (6 years). Information of treatment after trial termination was not provided. Given the age of typical statin initiators, 20 years seem like a realistic duration for statin treatment until end of life.

A large proportion of patients receive statins as secondary prevention initiated late in life, for example, by having their first acute myocardial infarction in their eighties. Our results indicate that with their limited life expectancy in mind, these patients are not likely to gain a substantial OP, regardless of their adherence. Støvring et al[17] estimated that lifelong statin treatment was associated with gains in survival ranging from 3 to 11 months.

A second limitation in our study is the varying trial duration between the trials. We have displayed the results both standardized and non-standardized. For the short-term trials, this implicates an assumption that the effect observed during the trial running time can be extrapolated to 5 years.

When assessing heterogeneity among the different outcomes, we found moderate-to-high heterogeneity. The degree of heterogeneity should be considered when evaluating the results. Moderate-to-high heterogeneity could indicate grouping of trials that do not examine the same biological effect, or that the patients included varies according to baseline characteristic, for example age, previous ischaemic heart disease or treatment type. Our aim was to estimate the overall effect of statins on cardiovascular and non-cardiovascular outcomes; therefore, we have chosen to display the results even though there is a moderate-to-high heterogeneity. By standardizing according to trial duration, the level of heterogeneity drops in Table 2. Furthermore, as shown in Figure S1A in the supplementary file, the level of heterogeneity decreases after subgrouping according to prevention type.

We envision three policy implications for the modelling of outcome postponement. Firstly, we suggest it should be calculated on all new trials to facilitate comparison of effects and incorporated into new guidelines. Secondly, it should be implemented in clinical practice when communicating treatment effects to patients. And finally, the use of outcome postponement could support prescribers in withholding treatment for patients with a short life expectancy or those who have proven intolerant. Future analyses of subgroups within trials might identify patients with a particularly large or small outcome postponement and thereby make it possible to target the optimal patient population better.

In conclusion, statin treatment did postpone cardiovascular events, but the effect magnitude was small when measured in outcome postponement.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr Hansen and Dr Hallas report grants from Pfizer, paid to our employer, outside the submitted work; Dr Hansen received speaking honoraria from Novartis outside the submitted work; Dr Pareek reports the following relationships—advisory board and speaking honoraria: AstraZeneca. The remaining authors have nothing to declare.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. They have all participated in drafting of the paper or revising it critically for important intellectual content. All authors have read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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