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Postponement of Death by Statin Use: A Systematic review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: The average postponement of the outcome (gain in time to event) has been proposed as a measure to convey the effect of preventive medications. Among its advantages over number needed to treat and relative risk reduction is a better intuitive understanding among lay persons.

Objectives: To develop a novel approach for modelling outcome postponement achieved within a trial's duration, based on published trial data and to present a formalized meta-analysis of modeled outcome postponement for all-cause mortality in statin trials.

Methods: The outcome postponement was modeled on the basis of the hazard ratio or relative risk, the mortality rate in the placebo group and the trial's duration. Outcome postponement was subjected to a meta-analysis. We also estimated the average outcome postponement as the area between Kaplan-Meier curves. Statin trials were identified through a systematic review.

Results: The median modeled outcome postponement was 10.0 days (interquartile range, 2.9-19.5 days). Meta-analysis of 16 trials provided a summary estimate of outcome postponement for all-cause mortality of 12.6 days, with a 95% postponement interval (PI) of 7.1-18.0. For primary, secondary, and mixed prevention trials, respectively, outcome postponement was 10.2 days (PI, 4.0-16.3), 17.4 days (PI, 6.0-28.8), and 8.5 days (PI, 1.9-15.0).

Conclusions: The modeled outcome postponement is amenable to meta-analysis, and may be a useful approach for presenting the benefits of preventive interventions. Statin treatment results in a small increase of average survival within the duration of a trial.

Systematic review registration:

The systematic review was registered in PROSPERO [CRD42016037507].

Introduction

One challenge in the practice of medicine lies in adequately explaining the effects of a proposed intervention to enable a patient to make an informed decision. With regards to preventive interventions, such as statin use, effect size is traditionally expressed as relative/absolute risk reductions or "number needed to treat" (NNT). However, such measures are not necessarily best for conveying intervention effect[1,2].

When contemplating preventative treatment, the additional time free of an undesirable clinical event can be considered more relevant. This average postponement of the study outcome represents an alternative to traditional effect measures for preventive treatment[3,4]. It has been shown that patients are responsive to outcome postponement, i.e. their chance of accepting the treatment changes increases when they are presented with higher values of outcome postponement[5]. On the other hand, even extreme differences in the presented values of NNT do not lead to greater or lower rates of treatment acceptance[6–8]. Moreover, NNT conveys a "lottery-like" understanding of how the treatment effect is distributed, potentially suggesting that the risk of death is influenced in only 1 in 40 treated patients. As statin treatment reduces cholesterol levels in nearly all treated patients[9] and a clear correlation between LDL cholesterol lowering and mortality has been demonstrated[10], it thus seems more plausible that statins slow atherosclerotic progression to some extent and thereby potentially delay death in all persons receiving treatment.

Methodologically, the average postponement accrued during a trial's duration can be estimated as the area between the survival curves for patients receiving the drug and placebo[4]. Kristensen et al[5]. recently published a systematic review of 11 randomized clinical trials of statin use, each including at least 1000 patients. They estimated that median postponement of all-cause mortality within the trial duration was 3.2 days for primary prevention and 4.1 days for secondary prevention[4]. However, their approach has two important weaknesses. First, a Kaplan-Meier survival curve for the outcome in question must be available. Second, measuring the area between survival curves does not allow for calculation of the variance of outcome postponement in the single trial, and thus outcome postponement cannot be subjected to meta-analysis using this approach.

In this study, we present a method for the meta-analysis of outcome postponement based on summary statistics from RCTs. We demonstrate the application of this method to estimate the average postponement of all-cause mortality based on meta-analysis of large placebo-controlled statin trials.

Methods

Data Sources and Searches

We searched Medline (search index date: May 1, 2015) using the following MeSH terms: statins, placebo, and random*. We also searched ClinicalTrials.gov (search index date: December 1, 2015) using the following terms: "statins" AND "placebo" (interventional). We further screened the reference lists of the included papers, but identified no additional studies for inclusion.

Study Selection

Our meta-analysis included randomized controlled trials of ≥1000 patients, in which a statin intervention (any type) was compared with placebo using a predefined primary or secondary outcome of death by any cause, and having a minimum trial follow-up of two years. Furthermore, we only used the original publication, i.e., we excluded sub-studies of the original trial, and we excluded trials which investigate a pediatric population (< 18 years). Lastly, we excluded trials that did not provide parameters required for postponement estimation. Initially we screened all abstracts for eligibility. We then extracted full-texts articles, which we categorized with reasons for exclusion (Table e1-online).

Data Extraction and Quality Assessment

Two authors (MRH and KGM) independently extracted trial characteristics and outcome data from each included trial. Any discrepancies were resolved by consensus. The extracted trial characteristics included the trial's duration; whether it represented primary, secondary or mixed intervention; and baseline LDL cholesterol level. The effect data included hazard ratio (HR) or relative risk (RR) and 95% confidence interval (CI), and the mortality rate or cumulative mortality in the placebo group. 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 of the patients had cardiovascular disease, and mixed prevention trials as trials including patients with and without cardiovascular disease. Two physicians independently performed trial classification.

The assessment of bias was performed using the Cochrane's risk of bias tool[11].

If the paper did not report an estimated mortality rate in the placebo group, we used the following hierarchy of alternative measures: a) the mortality rate among patients randomized to placebo as calculated by us based on the number of randomized patients, number of outcomes, and average

follow-up; b) the cumulative mortality among patients randomized to placebo as reported in the paper; c) the cumulative mortality among patients randomized to placebo as determined from the Kaplan-Meier survival curve; and d) the mortality rate among patients randomized to placebo, as calculated by us based on the number of randomized patients, number of events, and median follow-up. The latter approach may overestimate or underestimate the mortality rate, depending on whether the median follow-up is higher or lower than the average.

For trials that reported relative risk (n = 6) 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 values are low, e.g. below 20%[11]. None of the six trials that reported RR had a cumulative mortality risk of >15%.

Data Analysis: Outcome postponement

We have calculated outcome postponement of death in each trial. Postponement is described by the area between survival curves. We have used two different methods, pixelcounting and our novel mathematical model to estimate this area, which equals the postponement (gain in time) achieved in the active group. For details about the methods behind estimation of postponement from the mathematical model and pixel counting see appendix A and B-online.

Data Analysis: Meta-Analysis

We performed a meta-analysis of the postponement of all-cause death using inverse variance weighting and random effects models (STATA 14, Stata Corp, Texas) and using postponement intervals in place of confidence intervals. In order to describe effect modification by trial characteristics, we grouped trials according to a) trial duration (>5 years vs < 5 years), b) primary vs. secondary intervention, c) reporting by HR vs. RR as effect measures for all-cause mortality, d) high vs. low overall risk of bias, e) trials with the highest vs. lowest reduction in LDL cholesterol after 1 year f), and whether or not the trial was terminated earlier than originally planned, g) according to potency of the statin (low, medium and high), h) The trials with the highest mortality-rate vs. the trials with the lowest mortality-rate. Moreover, we added a post-hoc subgroup analysis comparing trials with high vs low degree of patient cross-over (for example, from placebo to statin). We further investigated reporting bias using a funnel plot.

To adjust for heterogeneity attributable to the varying durations of the trials, we standardized

the trial duration to five years in the modeled postponement. Essentially, this modeled the area between survival curves for five years of trial duration, based on the actually observed hazard ratio and cumulative mortality among untreated patients. Appendix C-online presents the equations used for standardization. Finally, to assist with interpretation of the postponement meta-analysis, we performed a HR-based meta-analysis of all-cause mortality.

The systematic review was registered in PROSPERO [CRD42016037507].

Results

Trial retrieval

We identified 115 potentially eligible trials, 16 of which met our inclusion criteria (Figure 1, Table e1-online). Kaplan-Meier survival curves were available for 8 of the trials, and all 16 trials presented the variables required to model the area between survival curves. Table 1 presents the trial characteristics (statin type, number of patients, trial duration and LDL status). Two (12.5%) were for primary prevention, six (37.5%) for secondary prevention, and eight (50%) for mixed prevention.

Outcome postponement

Table 2 presents the estimated outcome postponement based on pixel counting and modeling. The median values were 10.6 days with the pixel counting method, and 8.9 days with the modeling method. We found strong agreement between these two methods, a slope of 0.95 with linear regression and a parametric Pearson correlation coefficient of r = 0.94. Across all trials, the summary estimate of outcome postponement was 12.6 days (PI, 7.1-18.0). The I^2 value was 59.5, indicating moderate heterogeneity ($P = .001$). After standardization to a trial duration of five years, the estimated summary outcome postponement for all trials was 12.8 days (PI, 8.9-16.7), and I^2 decreased to 22.3% which was no longer statistically significant ($P = .179$) (Figure 2).

Subgroups

Table 3 shows the results of subgroup analyses by trial characteristics. Briefly, the modeled outcome postponement was 10.2 days (PI, 4.1-16.3) for primary prevention, 17.4 days (PI, 6.0-28.8) for secondary prevention, and 8.5 days (PI, 1.9-15.1) for mixed prevention. HR-based meta-analyses produced a summary HR of 0.89 (CI, 0.84-0.94) for all trials, 0.78 (CI, 0.67-0.92) for primary prevention trials, 0.85 (CI, 0.75-0.96) for secondary prevention trials, and 0.92 (CI, 0.88-0.97) for mixed prevention trials (Figure 3).

Risk of bias

All included trials were large, and had published or accessible protocols, concealed allocation, and blinding. All trials had a low overall risk of bias as determined using the Cochrane risk of bias tool. [11] Treatment switches were a possible concern, as some trials reported that considerable proportions of patients (range, 4.8-25.4%) assigned to the placebo group switched to statin treatment, or were assigned to the statin group but stopped their treatment. Outcome postponement was 11.6 days (PI, 5.1-18.1) in the ten trials with high cumulative incidence (>4%) of treatment switches, 36.5 days (PI, 19.9-53.2) in the single trial with a low degree of switching, and 10.4 days (PI, 3.0 – 17.8) in the 5 trials with an

unclear degree of switching.

Discussion

Here we investigated the effects of statin treatment on postponement of death, and performed a meta-analysis. We found that statin treatment resulted in a small average increase of survival within the trials' duration. Meta-analysis of 16 large RCT's revealed a survival gain of 12.6 days (PI, 7.1-18.0) within the trial duration. We stratified on prevention type, and demonstrated the largest postponement among the trials with secondary prevention, 17 days compared to 10 and 9 days in the primary and mixed prevention group. We expected this result, as the largest relative risk reduction has previously been found in this group[10]. We examined the effect of trial duration on postponement, and found a much larger postponement among the trial´s with a trial duration of five years and above, compared to below 5 years (19 days vs. 6 days). The difference nearly disappeared after standardization (14 days vs 11 days), demonstrating the strong dependency of outcome postponement on trial duration. The proposed model has several important strengths. The model-derived area between survival curves showed strong agreement with the area between survival curves as measured by pixel counting. Additionally, the model does not require a Kaplan-Meier survival curve to determine the outcome postponement, increasing the applicability of this method to a wider range of trials. Lastly, the use of a confidence interval proxy for outcome postponement enabled meta-analysis.

The postponement of death from other interventions vary greatly. One recent review on medical interventions for cancer, approved by the EMA from 2009-13, showed that only 51% of the drugs postponed death at all. The median follow-up was 5.4 years[12]. A different study evaluated the effects of regular exercise and a calorie restricted diet in healthy males, demonstrating a postponement of death by 6.2 month. Lastly, smoking cessation in a high-risk population postponed death by around 31 months[4].

As a tool for conveying treatment effects to patients, the concept of outcome postponement has important advantages over the number needed to treat (NNT). Most importantly, outcome postponement achieves greater responsiveness from patients. Surveys demonstrate that patients have the same likelihood of accepting a hypothetical treatment across NNT values ranging from 10 to 400[13,14]. On the other hand, patients presented with benefits conveyed in terms of outcome postponement clearly discriminate between efficient and less-efficient treatments. Additionally, an NNT value may be criticized for conveying a "lottery-like" understanding of how treatment effect is

distributed—for example, an NNT value of 40 could be wrongfully interpreted as meaning that 1 in 40 patients will experience all of the benefits treatment, while the remaining 39 experience no effect.

The most important clinical limitation of our model is that it does not capture the outcome postponement accrued after trial termination. Estimation of such benefits is difficult, and heavily relies on untestable assumptions. For example, Marshall used extrapolations from the LIPID trial to estimate the gain in life expectancy from lifelong statin treatment (i.e., for the rest of their lives), and arrived at a gain of 7.9 years. However, Chang et al. used the same data in a different model and estimated a gain of 3.0 years[15]. Using a model that incorporated mortality in different risk strata, Støvring et al. [16] estimated that lifelong statin treatment was associated with survival gains ranging from 3 to 11 months. Franco et al.[17] used life-table techniques, and reported outcome postponements of 2.0 and 2.4 years for lifelong statin use starting from 40 and 60 years of age, respectively. Some of these models apply the strong assumption that HR remains constant throughout the subject's lifetime, and most assume that all subjects can maintain lifelong statin treatment, which has been established as unrealistic in nearly all drug utilization studies[18,19]. Using our presently described method, we modeled the mortality outcome postponement in a recent study that provides Kaplan-Meier curves for 20 years of follow-up of the WOSCOPS trial, estimating an outcome postponement of 152 days (PI, 70-236 days)[20]. Given the uncertainties of estimating survival gain after trial termination, it is important to emphasize that our calculated outcome postponement is that achieved within the trial's duration, and should be considered an underestimate of the full outcome postponement including all post-trial follow-up. There is also a possibility of error by assuming that the survival curves would conform to an exponential decay function within the trial's running time or that this assumption is violated by the standardization to 5 years. However, the fact that there is good agreement between modeled postponement and postponement measured by pixel counting suggests that such violations are insignificant.

Other models have been proposed for estimating and presenting outcome postponement during a trial's duration. Lytsy[21] described a "delay of events" model that essentially estimates the average outcome postponement among patients who experienced the outcome, rather than among all patients randomized to receive treatment as in our model. The estimated outcome postponement in the 4S study[22] which they used as motivating case, was 1.0 year, which was larger than our estimate of 36.5 days. Notably, the "delay of event" measure seems to have little clinical utility, as it only applies to patients who die during the course of the trial, e.g. a population that cannot be identified at baseline. Additionally, Royston and Parmar[23,24] developed the concept of restricted mean survival time (RMST), which generalizes outcome postponement. The RMST approach is fully developed from a theoretical

and practical point of view, and it is the method of choice if data are available at the individual level.

From a clinical viewpoint, it would be a cautious and pragmatic approach to offer statins in accordance with the prevailing guidelines, i.e., as secondary prevention for all patients with manifest atherosclerotic disease and as primary prevention for certain high-risk patients. Statins are inexpensive, usually well tolerated,[25] and show a favorable cost-utility.[26] Based on the present evidence that statins do not have a large effect on postponement of all-cause mortality within a trial's duration, physicians and patients may be more inclined to discontinue treatment in patients showing intolerance to statins or having a short life expectancy.

In summary, we have developed a simple method for estimating outcome postponement based on summary measures that are almost universally available. This method is amenable to meta-analyses, and we believe that it may be a useful approach to presenting the benefits of preventive interventions to patients. We envisioned outcome postponement used as complementary to the prevailing measures. With regards to the subject matter in our present meta-analysis, statin treatment resulted in a small gain in average survival within the trials' duration. However, statins reduce the risk of cardiovascular outcomes, which could add value to the drug, from the patient's perspective, irrespective of the effect on all-cause mortality.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf: The authors declare that they do not have a conflict of interest.

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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Table 1. Characteristics of the Included Trials

Trial name	Statin and dose	Details of trial population	Type of prevention	Number of patients		Trial duration (years)	Baseline LDL-C (mg/dl) [10]	LDL-C difference at 1 year, compared to baseline (mg/dl)
				Statin	Placebo			
ASCOT-LLA[27]	Atorvastatin 10 mg	63 y (mean), 96% white, 19% women	Mixed	5168	5137	3.5	133.2	-41.4
CARDS[28]	Atorvastatin 10 mg	62 y (mean), 94.5% white, 32 % women	Primary	1428	1410	4.8	117.2	-44.1
JUPITER[29]	Rosuvastatin 20 mg	66 y (median), 71 % white, 38 % women	Primary	8901	8901	4.5	104.4	-42.2
WOSCOPS[30]	Pravastatin 40 mg	55 y, NA % white, 0 % women	Mixed	3302	3293	5.8	191.8	-41.4
4S[22]	Simvastatin 10-40 mg	35-70 y, NA % white, 18.5 % women	Secondary	2221	2223	5.9	188.7	-68.4
GISSI-HF[31]	Rosuvastatin 10 mg	68 y (mean), NA % white, 23 % women	Mixed	2285	2289	4.5	118.3	-35.6
LIPID[32]	Pravastatin 40 mg	62 y (median), NA % white, 17 % women	Secondary	4512	4502	6.2	150.0	-39.8
CORONA[33]	Rosuvastatin 10 mg	73 y (mean), NA % white, 24 % women	Secondary	2497	2514	3.0	137.8	NA
4D[34]	Atorvastatin 20 mg	66 y (mean), NA % white, 46 % women	Mixed	619	636	6.0	125.7	-34.4
ALERT[35]	Fluvastatin 40 mg	50 y (mean), NA % white, 34 % women	Mixed	1050	1052	6.0	160.1	-32.5
AURORA[36]	Rosuvastatin 10 mg	64 y (mean), 85 % white, 38 % women	Mixed	1389	1384	5.0	99.8	-38.3
CARE[37]	Pravastatin 40 mg	59 y (mean), 92.5 % white, 14 % women	Secondary	2081	2078	5.5	138.4	-39.8
HPS [38]	Simvastatin 40mg	40-80y, NA % white, 33 % women	Mixed	10269	10267	6	130.7	-49.9
LIPS[39]	Fluvastatin 80 mg	60 y (mean), NA % white, 16 % women	Secondary	844	833	4.0	132.3	-35.6
PROSPER[40]	Pravastatin 40 mg	75 y (mean), NA % white, 51 % women	Mixed	2891	2913	3.7	146.6	-40.2
SPARCL[41]	Atorvastatin 80 mg	63 y (mean), NA % white, 32 % women	Secondary	2365	2366	6.0	133.0	NA

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

Table 2. Results of Outcome Postponement Calculations

Trial name	HR/RR	Mortality rate in placebo arm§	Trial duration (years)	Postponement based on Kaplan-Meier survival curves, days	Modeled postponement, days (95% PI)	Modeled postponement standardized to 5 years, days (95% PI)
ASCOT-LLA[27]	0.87 (0.71 - 1.06)	1.3*	3.5	2.1	3.6 (-1.7 - 8.1)	7.3 (-3.3 - 16.3)
CARDS[28]*	0.73 (0.52 - 1.01)	1.5*	4.8	17.1	16.5 (-0.6 - 29.4)	17.8 (-0.7 - 31.8)
JUPITER[29]	0.80 (0.67 - 0.97)	1.3*	4.5	9.0	8.9 (1.3 - 14.8)	11.0 (1.6 - 18.1)
WOSCOPS[30]*	0.78 (0.60 - 1.00)	0.8	5.8	12.2	11.0 (0.0 - 20.0)	8.2 (0.0 - 14.9)
4S[22]	0.70 (0.58 - 0.85)	2.01	5.9	27.9	36.5 (18.2 - 51.4)	26.9 (13.4 - 37.8)
GISSI-HF[31]	1.00 (0.90 - 1.12)	8.0*	4.5	-11.7	0.0 (-28.1 - 24.1)	0.0 (-33.7 - 29.0)
LIPID[32]*	0.78 (0.69 - 0.87)	2.3	6.2	24.5	32.7 (19.3 - 46.3)	21.6 (12.7 - 30.5)
CORONA[33]	0.95 (0.86 - 1.05)	12.2*	3.0	5.8	7.9 (-7.8 - 22.4)	18.9 (-18.5 - 53.8)
4D[34]	0.93 (0.79 - 1.08)	12.7	6.0	NA	36.4 (-40.1 - 112.9)	27.2 (-30.2 - 84.0)
ALERT[35]*	1.02 (0.81 - 1.31)	2.6	6.0	NA	-3.1 (-46.6 - 29.3)	-2.1 (-32.9 - 20.6)
AURORA[36]	0.96 (0.86 - 1.07)	14.0*	5.0	NA	16.4 (-28.0 - 58.7)	16.4 (-27.9 - 58.5)
CARE[37]*	0.91 (0.74 - 1.12)	1.9	5.5	NA	8.8 (-11.6 - 25.5)	7.3 (-9.6 - 21.1)
HPS[38]*	0.87 (0.81 - 0.94)	2.9	6	NA	22.5 (10.3 - 33.0)	15.9 (7.3 - 23.3)
LIPS[39]*	0.69 (0.45 - 1.07)	1.5	4.0	NA	13.2 (-3.0 - 23.5)	20.4 (-4.6 - 36.4)
PROSPER[40]	0.97 (0.83 - 1.14)	3.3	3.7	NA	2.3 (-10.5 - 13.0)	4.0 (-18.6 - 23.0)
SPARCL[41]	1.00 (0.82 - 1.21)	1.8	6.0	NA	0.0 (-23.2 - 20.2)	0.0 (-16.3 - 14.1)

Abbreviations: NA, not available; HR, hazard ratio; RR, relative risk; PI, postponement interval.
*RR used instead of HR.
§Mortality-rate per 100 person-years at risk.
*Mortality-rate reported in the paper or provided by the author's (GISSI-HF), the remaining mortality-rates have been calculated as indicated in the method section.

Table 3. Subgroup Meta-Analyses of Postponement of All-Cause Mortality According to Trial Characteristics

Subgroup	Number of trials	Outcome post-ponement, days (95% PI)	I^2	Outcome postponement standardized to five years, days (95% PI)	I^2	HR-based meta-analysis, HR (95% CI)	I^2
All trials	16	12.6 (7.1 - 18.0)	60	12.8 (8.8 - 16.7)	22	0.89 (0.84 - 0.94)	47
Primary prevention	2	10.2 (4.1 - 16.3)	0	12.4 (5.0 - 19.8)	0	0.78 (0.67 - 0.92)	0
Secondary prevention	6	17.4 (6.0 - 28.8)	67	16.2 (7.4 - 25.1)	50	0.85 (0.75 - 0.96)	66
Mixed prevention	8	8.5 (1.9 - 15.0)	39	10.0 (5.5 - 14.5)	0	0.92 (0.88 - 0.97)	12
Trial duration < 5 years	7	6.3 (2.9 - 9.7)	0	10.7 (5.4 - 16.0)	0	0.91 (0.84 - 0.99)	33
Trial duration ≥ 5 years	9	18.6 (9.5 - 27.7)	52	13.6 (7.3 - 19.9)	47	0.88 (0.81 - 0.94)	52
Early trial termination	3	18.6 (4.0 - 33.3)	79	16.4 (9.1 - 23.6)	33	0.78 (0.71 - 0.86)	0
Planned trial termination	13	10.8 (4.7 - 16.8)	51	11.3 (6.6 - 15.9)	17	0.91 (0.87 - 0.96)	35
High degree of switching between groups*	10	11.6 (5.1 - 18.1)	64	12.7 (8.4 - 16.9)	13	0.88 (0.84 - 0.93)	27
Unclear degree of switching between groups	5	10.4 (3.0 - 17.8)	0	8.7 (2.1 - 15.2)	0	0.95 (0.86 - 1.04)	28
Low degree of switching between groups	1	36.5 (19.9 - 53.2)	.	27.0 (14.7 - 39.2)	.	0.70 (0.58 - 0.85)	.
Trials with the least LDL reduction at 1 year*	5	10.3 (-0.5 - 21.1)	0	11.1 (-2.2 - 24.5)	0	0.97 (0.90 - 1.03)	0
Trials with the greatest LDL reduction at 1 year	9	14.7 (7.5 - 21.9)	77	13.7 (9.1 - 18.4)	41	0.83 (0.78 - 0.89)	28
High potency statins	6	8.1 (2.3 – 13.7)	0	8.92 (2.1 - 15.8)	0	0.95 (0.90 - 1.00)	0
Medium potency statins	5	17.3 (5.6 - 29.0)	82	16.6 (9.8 - 23.4)	37	0.81 (0.73 - 0.90)	33
Low potency statins	5	12.35 (0.4 - 24.3)	68	10.8 (2.8 - 18.9)	46	0.88 (0.78 - 0.99)	47
Trials with the highest mortality-rate	8	13.9 (3.3 - 24.5)	56	16.5 (10.8 - 21.6)	0	0.92 (0.87 - 0.98)	24
Trials with the lowest mortality-rate§	8	11.2 (5.1 - 17.4)	59	11.6 (6.2 - 16.9)	38	0.82 (0.75 - 0.90)	50

Abbreviations: HR, hazard ratio; PI, postponement interval.
*High incidence of switching was defined as above 4%.
*Threshold for highest reduction was defined as ≤ 39.8 mg/dl. Two trials did not report LDL reduction.
§ Threshold for lowest mortality-rate was defined as ≤ 0.022 per 100 person-years at risk (median).

Figure 1. Flowchart of search to identify randomized, placebo-controlled statin trials

Figure 2. Forest Plots of Postponement of All-Cause Mortality

Figure 3. Forest Plot of Hazard Ratios in the Trials

1 E-supp Figure 4. Funnel Plots of hazard ratios for Investigation of Publication Bias

Appendix A – Method section on estimation of Postponement

Data Analysis: Postponement of Death in Single Trials

We calculated postponement of death in each single trial by mathematical modeling of the area between survival curves, which provided both a point estimate and the corresponding transformation of the original confidence interval. We then used linear regression in addition to Pearson's correlation to compare the model-derived estimate with the estimates derived by pixel counting.

Estimation of Postponement by Mathematical Modeling

The model-derived outcome of postponement accrued during the trial's duration is given by the following equation:

$$\mathrm{OP} = \frac{-e^{-HR*k_0*t_s}+(HR*e^{-k_0*t_s})+1-HR}{HR*k_0}$$

where t_s is the time of trial termination, k_0 is the mortality rate among untreated patients, and HR is the hazard ratio for outcome in treated vs untreated patients. Appendix C presents the derivation and details of the equation, together with the equations employed to model the outcome postponement from cumulative mortality, when mortality rates were unavailable.

The underlying assumption of the model is that the mortality rates are stable in both treatment arms throughout the duration of the trial. To calculate the upper and lower postponement limits of the modeled area between survival curves, we simply substituted the HR in the equation with the upper and lower confidence limit of the estimated HR. This transformed interval, termed the postponement interval (PI), is consistent with respect to the direction and preservation of the critical value. In other words, HR confidence limits below/above 1 are transformed into outcome postponement limits above/below 0, and an HR limit of 1 (implying no effect) is transformed into 0 days' postponement. This also applies to the use of confidence limits other than 95%. Owing to the differences in weighting, meta-analytic estimates may show minor inconsistencies regarding critical values. It remains to be established whether the PI can formally be interpreted as a confidence interval, for example whether it provides 95% coverage of the underlying parameter.

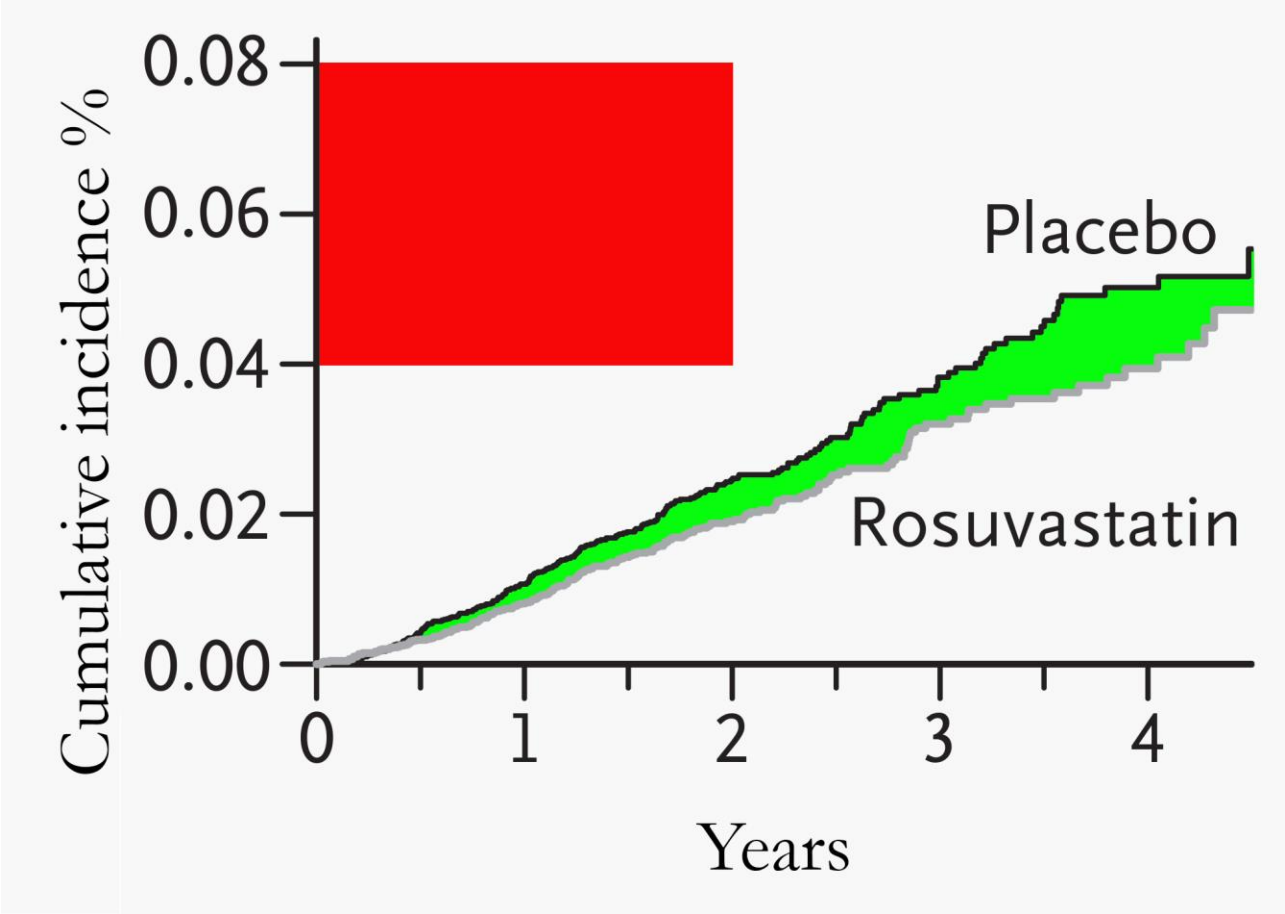
Estimation of Postponement by Pixel Counting

When a Kaplan-Meier survival curve for all-cause mortality was available for a trial, we estimated the area between survival curves by counting pixels, as previously described[5]. Briefly, we magnified the original Kaplan-Meier curve and imported it into a graphics software program (Adobe Photoshop CS6, Adobe Systems). An example of this approach is given in appendix B. When the primary publication of

a trial did not include a Kaplan-Meier survival curve for all-cause mortality (n = 7), we contacted the study authors and asked them to provide one. We received no responses.

Appendix B

Example of Calculation of Outcome Postponement by Pixel Count, Jupiter Study



The text in this figure has been modified from the original.

1. This graph was copied from the published article in PDF format to the Photoshop program. A reference area was drawn using straight lines with the ruler tool: here at a follow-up of 0-2 years on the x-axis and at 4-8% cumulative risk on the y-axis (red box). A vertical line was drawn at 4.5 years to represent the right border of the area between survival curves.. Using the magic wand tool, we found the size of the two areas in pixels.

In this example:

Reference area size: 312,308 pixels
Size of area between survival curves: 96,148.5 pixels

3. The average postponement of death was calculated as:

$$\frac{(Pixel\ count\ (area\ between\ curves) * \Delta y\ (reference\ area) * \Delta x\ (reference\ area)}{Pixel\ count\ (reference\ area)}$$

In this example:

$$\frac{96{,}148.5 * 0.04 * 2\ years}{312308} * 365.4\ days/year = 9.0\ days$$

E-supp Appendix C

Computing the Area Between Survival Curves Using an Exponential Decay Function

If we assume that the mortality rate is constant over the duration of the trial, then the survival function among untreated patients is given by an exponential decay function:

$$S_0 = e^{-k_0 t}$$

where k_0 is the mortality rate among untreated patients.
Similarly, the survival among treated patients is given by

$$S_1 = e^{-k_1 t}$$

If t_s is the time of trial termination, m_0 is the cumulated proportion of deaths among untreated patients at t_s, and HR is the hazard ratio for outcome in treated vs untreated patients, then:

$$e^{-k_0 * t_s} = 1 - m_0 \quad \text{and}$$

$$k_0 = \frac{-\ln(1-m_0)}{t_s} \qquad (1)$$

If we assume that

$$HR \cong \frac{k_1}{k_0}$$

then the outcome postponement (OP) accrued during the trial is given by

$$OP = \int_{t=0}^{t_s} (s_1 - s_0)$$

$$= \int_{t=0}^{t_s} (e^{-HR*k_0*t} - e^{-k_0*t})$$

$$= {}_{0}^{t_s}\left[\left(\frac{-1}{HR*k_0}\right) * e^{-HR*k_0*t} + \frac{1}{k_0} * e^{-k_0*t}\right]$$

$$= \left(\frac{-1}{HR*k_0}\right) * e^{-HR*k_0*t_s} + \frac{1}{k_0} * e^{-k_0*t_s} + \frac{1}{HR*k_0} - \frac{1}{k_0}$$

$$= \frac{-e^{-HR*k_0*t_s} + (HR*e^{-k_0*t_s}) + 1 - HR}{HR*k_0} \qquad (2)$$

If the mortality rate among untreated patients (k_0) is reported, then the 5-year standardized outcome postponement is calculated simply by using t_s = 5 years in equation (2).

If k_0 is unavailable, it can be derived from equation (1), provided that the cumulative mortality (m_0) is available.

The upper and lower limits of the postponement interval can be determined by substituting HR, with its upper and lower confidence limits, in the calculations above.

1 Table 1e. All Excluded Trials, With our Reason for Exclusion

2

First author, year	Pubmed ID	Reason for exclusion							
		No statin	<1000 patients	No placebo	Substudy of an included study	Non-randomized study	<2 years of follow-up	Patients < 18 years of age	Lack parameters for estimating outcome postponement
Agema et al, 2004	15068395				X				
Albert et al, 2001	11434828						X		
Albert et al, 2001	11376301						X		
Alkhenizan, 2003	12836863					X			
Amarenco et al, 2009	19461031				X				
Amarenco et al, 2009	19228842				X				
Amarenco et al, 2010	20110538				X				
Anderssen et al, 2005	15694949		X						
Anonymous 2002	12114036								X
Anonymous 2007	17398372				X				
Anonymous, 1993	8213583						X		
Anonymous, 1994	8163252						X		
Anonymous, 1997	9254773					X			
Anonymous, 2002	12532550					X			
Anonymous, 2005	17228404		X						
Anonymous, 2005	15771782				X				
Anonymous, 2005	16138641				X				
Arad et al, 2001	11578788				X				
Arad et al, 2005	15992652	X							
Arampatzis et al, 2005	15846273				X				
Asselbergs et al, 2004	15492322		X						
Asselbergs et al, 2005	15692120				X				
Atthobari et al, 2006	16720593					X			
Bays et al, 2004	15639688						X		
Bennet et al, 2004	15650343						X		
Boekholdt et al, 2003	12742999				X				
Bone et al, 2007	17726081		X						
Bulbulia et al, 2011	22115874				X				
Byington et al, 1995	7586340					X			
Cohen et al, 2000	10740160				X				
Collins et al, 2004	15016485				X				
Colomb et al 2004	15020036						X		
Criner et al, 2014	24836125		X						
Crouse et al, 2004	15229392				X				
Crouse et al, 2007	17384434		X						
De Groot et al, 1995	7572685		X						
Deedwania et al, 2007	17283260						X		
Devaraj et al, 2006	16968805						X		
Di Padova et al, 1984	6083597		X						
Downs et al, 1998	9613910			X					
Emberson et al, 2011	21277016				X				

Fellstrom et al, 2004	15458450				X				
Fellstrom et al, 2006	17100723				X				
Flaker et al, 1999	10399998				X				
Furberg et al, 1994	7734010		X						
Gentile et al, 2000	11225965						X		
Glynn et al, 2009	19329822				X				
Goldberg et al, 2004	15132403						X		
Goldstein et al, 2009	19745172				X				
Herd et al, 1997	9264419		X						
Herrmann et al, 2006	16490024		X						
Holdaas et al, 2005	15784644				X				
Hunt et al, 2001	11352694				X				
Jukema et al, 1995	7743614				X				
Jukema et al, 1996	8630669				X				
Kastelein et al, 2005	15846260				X				
Keane et al, 2001	11158861				X				
Keech et al, 1994	8005129		X						
Keech et al, 1996	8904621		X						
Knopp et al, 2006[A]	16801565								X
Krane et al, 2008	18818679				X				
LaRosa et al, 1994	8122946		X						
Lee et al, 2004	15367512				X				
Lemos et al, 2005	15708183				X				
Lewis et al, 1998	9841599				X				
Maitland et al, 2006	16869455				X				
Mancia et al, 2010	20339154				X				
Manfrini et al, 2004	15165921		X						
Marchioli et al, 2009	19589110				X				
Marcovecchio et al, 2009	20017932							X	
Margolis et al, 2014	24595629			X					
Mose et al, 2014	24256611		X						
Mukamal et al, 2006	16651056			X					
Norby et al, 2009	19333947				X				
Olsson, 2001	11383378		X						
Ostadal et al, 2005	15790413				X				
Peters et al, 1993	8297542					X			
Peters et al, 2011	21617330				X				
Peters et al, 2012	21982737				X				
Pfeffer et al, 1995	7572695				X				
Plehn et al, 1999	9892586				X				
Poli et al, 1999	10546121				X				
Probstfield et al, 1995	7572686		X						
Ridker et al, 2009	19329177				X				
Rogers et al, 2014	24952697				X				
Saia et al, 2004	14697476				X				
Sever et al, 2004	15765890				X				
Sever et al, 2009	19232755				X				
Soedamah-Muthu et al, 2015	25899452				X				
Stein, 1998	9737645					X			

Stein, 1998	9811154					X			
Svilaas et al, 2004	14743227					X			
Tan et al, 1999	10532516		X						
Tobert et al, 1990	2180268					X			
Trompet et al, 2010	19653027				X				
Van Boven et al, 1996	8840836				X				
Van der Harst et al, 2005	16275178		X						
Vladimirova-Kitova et al, 2012	22108444						X		
White et al, 2000	10922421				X				
Zanchetti et al, 2004	15514192		X						

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