

BMJ Open The effect of statins on average survival in randomised trials, an analysis of end point postponement

Malene Lopez Kristensen,¹ Palle Mark Christensen,¹ Jesper Hallas^{1,2}

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ABSTRACT

Objective: To estimate the average postponement of death in statin trials.

Setting: A systematic literature review of all statin trials that presented all-cause survival curves for treated and untreated.

Intervention: Statin treatment compared to placebo.

Primary outcome measures: The average postponement of death as represented by the area between the survival curves.

Results: 6 studies for primary prevention and 5 for secondary prevention with a follow-up between 2.0 and 6.1 years were identified. Death was postponed between –5 and 19 days in primary prevention trials and between –10 and 27 days in secondary prevention trials. The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively.

Conclusions: Statin treatment results in a surprisingly small average gain in overall survival within the trials' running time. For patients whose life expectancy is limited or who have adverse effects of treatment, withholding statin therapy should be considered.

INTRODUCTION

HMG-CoA reductase inhibitors—or 'statins'—are important drugs for the prevention of atherosclerotic conditions such as stroke, myocardial infarction or limb ischaemia.¹ Current guidelines indicate that statins should be prescribed to all patients manifesting ischaemia and to other patients at high risk,^{1 2} and that statins are among the most widely prescribed drugs overall.³

The magnitude of their preventive effect is controversial; also controversial is how such effects should be conveyed to the patients.⁴ The number needed to treat (NNT) has been widely endorsed as a useful effect measure for clinical practice. Its popularity is based on the belief that the NNT conveys drug effects to physicians and their patients in a single, easily understood measure.⁵ However, it has been shown that patients^{6–9}—and to some extent prescribers¹⁰—are not responsive to the NNT value, that is, their choices of whether or not

Strengths and limitations of this study

- This is the first study ever to systematically evaluate statin trials using average postponement of death as the primary outcome.
- We have only estimated the survival gain achieved within the trials' running time, whereas in real life, treatment is often continued much longer.
- We have only focused on all-cause mortality. Other outcomes may also be relevant, for example, non-fatal cardiovascular end points.

to take or to prescribe the drug are largely unaffected by the NNT values given. Also, NNT may be criticised for not conveying a plausible model for how the benefit of statins is distributed.¹⁰ The thinking behind NNT suggests a lottery-like model, where, for example, 1 patient in 40 receives full benefit from the drug, while in the remaining 39 patients, it has no effect. It is more plausible that statins will delay atherosclerotic progression in all those treated, to an extent where 1 in 40 patients will have his or her end point postponed until after the outcome is measured. The remaining 39 patients will also have their end points postponed, but none to an extent where they cross this timeline. As an alternative to the NNT, it has been suggested that the drug benefit may be conveyed by an estimate of the average postponement in the occurrence of the end point for all treated.⁴ It has been shown that patients are more responsive to values of postponement than to values of NNT.⁷ Technically, the average postponement can be calculated as the area between the survival curves for the treated and the untreated.¹¹

To the best of our knowledge, statins have not been systematically assessed in an outcome postponement model. We identified statin trial reports that provided all-cause survival curves for treated and untreated, and calculated the average postponement of death as represented by the area between the survival curves.



¹Department of Clinical Pharmacology, University of Southern Denmark, Odense, Denmark

²Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

Correspondence to Professor Jesper Hallas; jhallas@health.sdu.dk

MATERIALS

Search and inclusion of trials

We based our study on a meta-analysis on the effect of statins on cardiovascular morbidity or survival, published by Baigent *et al.*¹² The Baigent paper had retrieved all relevant papers published until the end of 2009. We supplemented the Baigent search and included the period 2010–2011. Our supplementary literature search yielded one further paper.¹³

The included trials in our analysis were defined by being randomised, having at least 1000 patients included, comparing a statin with no treatment or placebo, having at least 2 years of follow-up, having all-cause mortality as a pre-specified primary or secondary end point and by providing a Kaplan-Meier plot of all-cause mortality in treated versus untreated in the publication. The 11 included papers are listed in table 1. We have listed the excluded papers in online supplementary appendix A, also giving the reason for exclusion.

ANALYSIS

An example of the technical aspects of area calculations is shown in online supplementary appendix B. In brief, we magnified the Kaplan-Meier graphs from the publications by 300% and imported them into Paint (Microsoft Windows V.7). Ten of 11 publications were available in electronically processed format, the last¹⁴ was available in a scanned copy. A vertical line was drawn at the cut point according to the original publication. A reference area was drawn in the lower left corner of the graph, using the tick marks of the x and y axes in the original graph. The number of pixels in the reference area was calculated by multiplying the measured number of pixels at the length and height of the drawn box. The graph was then imported into Adobe Photoshop (Adobe Systems, San Jose, California, USA), and the number of pixels between the survival curves was counted using the polygonal lasso tool. We counted the area in segments, with better survival in the untreated group as negative, and we used the cut point as the right border of the area between survival curves. If no cut point was given, we used the latest time both survival curves were drawn in the original Kaplan-Meier plot. If more than one cut point was used in the original publication, we chose the latest. All area calculations were carried out in triplicate by three independent observers, to assess the variance of the area calculations.

We also calculated all areas in a less technical manner, that is, by drawing one or more triangles by hand on magnified paper prints of the survival curve for each study and then calculating the areas of these triangles by standard arithmetic. This is referred to as the quick method.

We categorised the studies as being in primary or secondary prevention, depending on whether the study included participants with manifest cardiovascular disease prior to randomisation. We calculated summary

estimates of ORs for all-cause mortality separately for included as well as excluded studies using a standard meta-analysis technique.¹⁵

RESULTS

Of the 26 publications provided in the original meta-analysis and the one retrieved by literature search, 11 could be included in our analysis. The most common reason for exclusion was lack of a KM survival plot for treated and untreated (9 studies). Among the included studies, six were on primary prevention and five were on secondary prevention.

The calculated end point postponement values are given in table 1, together with the effect measures provided in the original publications. Death was postponed between –5 and 19 days in primary prevention trials and between –10 and 27 days in secondary prevention trials. The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively.

The quick method provided estimates that deviated from the pixel count method by <1 day in 7 of 11 trials (64%). The maximum difference between the two methods was 4.8 days, for the 4S trial (table 1).

The summary OR for all-cause mortality from the included trials was 0.89 (CI 0.84 to 0.93), compared to 0.91 (CI 0.86 to 0.96) for the excluded trials.

DISCUSSION

To the best of our knowledge, statin trials have not previously been subjected to a systematic assessment of survival gain by this technique. The survival gains we found are surprisingly small. The highest value was 27 days, found in the 4S study, achieved by 5.8 years of simvastatin therapy in participants with a history of unstable angina or myocardial infarction. Experience from studies of preferences, when presented with similar scenarios, shows that as many as 70% of lay persons would not accept such a treatment.¹⁶

There are a number of caveats that need to be considered. First, this analysis only estimates the survival gain achieved within the trials' running time. After termination of the trials, the treated would continue to accrue survival gain as long as there was a difference in cumulative mortality between the treatment arms. There are a few studies with long-term follow-up after cardiovascular intervention trials showing that this survival might be substantial,¹⁷ but there are also studies showing that mortality becomes similar in the two groups after the trial's termination.¹⁸ Some modelling studies have suggested a large survival benefit with long-term treatment beyond the trial's running time,¹⁹ but obviously this conclusion relies heavily on model assumptions. Second, our analysis is based on the assumption that survival gain is uniform among the treated. The true distribution is unknown, and some authors have suggested that a hybrid model of classical NNT thinking along with a

Table 1 Estimated postponement of death in 11 trials comparing statin therapy with no treatment or placebo

| Study ID, reference, publication year | Number included | Intervention/comparator | Prevention | Cut point, years | Dead: statin/control, % | RR (95% CI) | NNT | Postponement, days (SD) | Postponement, quick method, days |
|---------------------------------------|-----------------|---------------------------------------|------------|------------------|-------------------------|---------------------|------|-------------------------|----------------------------------|
| ALLHAT-LLT ²² 2002 | 10 355 | Pravastatin (40 mg) vs usual care | Primary | 6 | 14.9/15.3 | 0.99 (0.89 to 1.11) | 250 | −4.96 (0.06) | −5.48 |
| ASCOT-LLA ²³ 2003 | 19 342 | Atorvastatin (10 mg) vs placebo | Primary | 3.5 | 3.6/4.1 | 0.87 (0.71 to 1.06) | 200 | 1.99 (0.04) | 1.94 |
| CARDS ²⁴ 2004 | 2838 | Atorvastatin (10 mg) vs placebo | Primary | 4.8 | 4.3/5.8 | 0.73 (0.52 to 1.01) | 66.7 | 18.66 (0.04) | 17.21 |
| JUPITER ²⁵ 2008 | 17 802 | Rosuvastatin (20 mg) vs placebo | Primary | 4 | 2.22/2.77 | 0.80 (0.67 to 0.97) | 31 | 7.26 (0.01) | 7.25 |
| MEGA ²⁶ 2006 | 7832 | Pravastatin (5–20 mg) vs no treatment | Primary | 5 | 1.11/1.66 | 0.68 (0.46 to 1.00) | 182 | 4.42 (0.01) | 4.47 |
| WOSCOPS ²⁷ 1995 | 6595 | Pravastatin (40 mg) vs placebo | Primary | 5 | 3.2/4.1 | 0.78 (0.60 to 1.00) | 111 | 9.33 (0.10) | 8.29 |
| 4S ²⁸ 1994 | 4444 | Simvastatin (10–40 mg) vs placebo | Secondary | 5.8 | 8.7/12.3 | 0.7 (0.58 to 0.85) | 27.8 | 27.18 (0.26) | 31.96 |
| GISSI-HF ²⁹ 2008 | 4631 | Rosuvastatin (10 mg) vs placebo | Secondary | 4.4 | 28.8/28.1 | 1.00 (0.90 to 1.12) | −143 | −9.51 (0.01) | −10.44 |
| GISSI-P ¹⁴ 2000 | 4271 | Pravastatin (20 mg) vs no treatment | Secondary | 2.0 | 3.37/4.13 | 0.84 (0.61 to 1.14) | 132 | 1.76 (0.07) | 2.53 |
| LIPID ³⁰ 1998 | 9014 | Pravastatin (40 mg) vs placebo | Secondary | 6.1 | 11.0/14.1 | 0.78 (0.69 to 0.87) | 32.3 | 22.05 (0.21) | 26.59 |
| CORONA ¹³ 2007 | 5011 | Rosuvastatin (10 mg) vs placebo | Secondary | 2.7 | 29.0/30.4 | 0.95 (0.86 to 1.05) | 71 | 4.09 (0.04) | 4.16 |

NNT, number needed to treat; RR, relative risk.

postponement model could be used.⁸ This model would convey something similar to 'simvastatin resulted in an average of 8 months' postponement of heart attacks for one of four patients'.⁸ Unfortunately, this model is highly speculative. There are no empirical clues as to what proportion of patients will have their outcome postponed. In addition, there is very limited experience about the extent to which the hybrid model is understood by patients and how it affects their choices. Third, we have only focused on all-cause mortality in our analysis. Other outcomes may also be relevant. For example, we calculated the area between Kaplan-Meier curves for 'any cardiovascular end point' in the 4S trial, and found an average postponement of 109 days. A systematic postponement analysis of end points other than all-cause mortality might thus be warranted. Fourth, we could only include 11 of 27 trials, and we need to consider the possibility that the low postponement values may be explained by selection bias. However, the summary estimates of ORs for all-cause mortality observed in the included or excluded trials do not indicate a better intervention effect in excluded trials. If anything, the included studies seem to have a marginally more favourable result.

There are a number of technical caveats as well. The method used to estimate the area between the Kaplan-Meier curves may seem too technical for routine use. However, it was reassuring to see that the quick-method produced nearly identical results. None of the quick-method estimates deviated more than 5 days from the pixel-count estimates, and most deviations were below 1 day. Also, on a technical note, the SEs provided in this paper refer to the area calculations alone and not to the overall effect of the intervention. For example, a single underpowered study is likely to have a HR in which CI crosses the null value. That the intervention is harmful cannot be ruled out from this study alone. Yet, the survival curves may show good separation, and the area between curves might be calculated with little uncertainty. Unfortunately, a statistical model has not yet been developed that incorporates the uncertainty of the net benefit of the drug, such as the CI of the HR, into a postponement model. Consequently, there are currently no methods to perform meta-analyses of outcome postponement.

What are the clinical implications of our findings? We believe that statins should be prescribed according to the prevailing guidelines. Statins are usually inexpensive and safe, at least in a clinical trial setting,²⁰ and the benefit in terms of mortality or non-fatal cardiovascular outcomes cannot reasonably be challenged. However, if the patient has intolerance or unpleasant side effects from statins, for example, muscular problems, physicians should not be too insistent on the patient continuing them. Also, for patients whose life expectancy is short, the benefit of statin therapy in terms of survival gain may be quite limited.²¹ The physician might consider using postponement measures to communicate the

benefit to the patients, instead of the NNT or relative risk reductions, which are so prone to misunderstanding. Admittedly, calculating postponement values may seem too technical for routine use by a typical prescriber. However, it is our hope that the postponement approach could be adopted by researchers or authors of guidelines as a supplementary mean of communicating drug benefit.

Contributors MLK and JH wrote the first draft of the manuscript. MLK performed the analyses and developed the pixel counting method. All the authors provided input to the study concept, analysis plan and editing the manuscript.

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