BMJ Open

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

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To cite: Kristensen ML, Christensen PM, Hallas J. The effect of statins on average survival in randomised trials, an analysis of end point postponement. *BMJ Open* 2015;**5**:e007118. doi:10.1136/bmjopen-2014-007118

▸ Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2014-007118).

Received 21 November 2014
Revised 29 April 2015
Accepted 7 May 2015

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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.

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.

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 prescribers[10]—are not responsive to the NNT value, that is, their choices of whether or not 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.

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 last[14] 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.

Funding The study is funded by University of Southern Denmark.

Competing interests JH has participated in research projects funded by Novartis, Pfizer and MSD, with grants paid to the institution where he was employed. He has personally received fees for teaching or consulting, from the Danish Association of Pharmaceutical Manufacturers and from Pfizer, Novartis and Astra Zeneca.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Raw data from this project can be made available by a request to the corresponding author.

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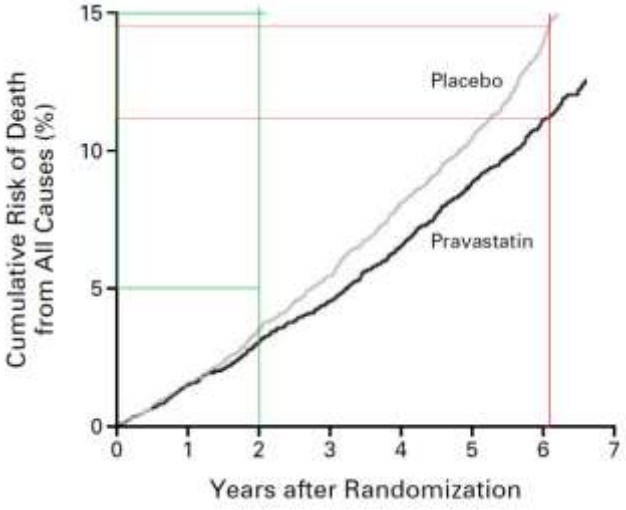
Appendix A

Statin trials excluded from the endpoint postponement analysis

Study	Reason for exclusion
Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238–48.	Kaplan-Meier plot on all-cause mortality was not published
Downs JR, Clearfi eld M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279: 1615–22.	All-cause mortality was not analyzed
Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003; 361: 2024–31.	Kaplan-Meier plot on all-cause mortality was not published
Koren MJ, Hunninghake DB. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipidlowering disease management clinics: the alliance study. J Am Coll Cardiol 2004; 44: 1772–79	Kaplan-Meier plot on all-cause mortality was not published
Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Effi cacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006; 29: 1478–85.	Kaplan-Meier plot on all-cause mortality was not published
de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004; 292: 1307–16.	More versus less aggressive statin therapy
Fellstrom BC, Jardine AG, Schmieder RE, et al, for the AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395–407.	Kaplan-Meier plot on all-cause mortality was not published
Sacks FM, Pfeff er MA, Moyé LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335: 1001–09.	Kaplan-Meier plot on all-cause mortality was not published
Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.	Kaplan-Meier plot on all-cause mortality was not published
Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005; 294: 2437–45.	More versus less aggressive statin therapy
Serruys PWJC, de Feyter P, Macaya C, et al, for the Lescol Intervention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. JAMA 2002; 287: 3215–22.	Kaplan-Meier plot on all-cause mortality was not published
The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997; 336: 153–62.	More versus less aggressive statin therapy

Shepherd J, Blauw GJ, Murphy MB, et al, on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–30.	Kaplan-Meier plot on all-cause mortality was not published
Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495–504.	More versus less aggressive statin therapy
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010; published online Nov 9. DOI:10.1016/S0140-6736(10)60310-8.	More versus less aggressive statin therapy
LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425–35.	More versus less aggressive statin therapy

Appendix B
Example of calculation of endpoint postponement, LIPID study.



1. The graph is copied from the published article in PDF format to the program Paint (300% zoom) where it is saved in bitmap format. A reference area is drawn by straight lines, using the tick marks of the graph, here 0-2 years follow-up on the x-axis and 5-15% cumulative risk on the y-axis (green box). A vertical line to represent the right border of the area between curves is drawn at 6.1 years (red line).
2. The graph is imported into Adobe Photoshop Elements 10, and the area in the reference area and between survival curves is redrawn by using the polygonal lasso tool. The size of the areas can be read directly. In this example:

Size of reference area: 106220 pixels
Size of area between survival curves: 32118 pixels

3. The average postponement of delay is calculated as:

Pixel count (area between curves) * Δy (reference area) * Δx (reference area) / Pixel count (reference area)

In this example:

32118 * 0.10 * 2 years / 106220 = 22.07 days

All analyses were carried out by three observers and the results are expressed as the average of these three individual observations.