

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}

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

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.

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.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

1. Psaty BM, Weiss NS. 2013 ACC/AHA guideline on the treatment of blood cholesterol: a fresh interpretation of old evidence. *JAMA* 2014;311:461–2.
2. Perk J, De Backer G, Gohlke H, *et al*. European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice version 2012. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635–701.
3. Simons J. The \$10 billion pill. *Fortune* 2003;147:58–62, 66, 68.
4. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728–33.
5. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310:452–4.
6. Halvorsen PA. What information do patients need to make a medical decision? *Med Decis Making* 2010;30(5 Suppl):11S–3S.
7. Christensen PM, Brosen K, Brixen K, *et al*. A randomized trial of laypersons' perception of the benefit of osteoporosis therapy: number needed to treat versus postponement of hip fracture. *Clin Ther* 2003;25:2575–85.
8. Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. *Ann Intern Med* 2007;146:848–56.
9. Halvorsen PA, Kristiansen IS. Decisions on drug therapies by numbers needed to treat: a randomized trial. *Arch Intern Med* 2005;165:1140–6.
10. Christensen PM, Kristiansen IS. Number-needed-to-treat (NNT)—needs treatment with care. *Basic Clin Pharmacol Toxicol* 2006;99:12–16.
11. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions—standardizing data on outcomes. *N Engl J Med* 1998;339:380–6.
12. Baigent C, Blackwell L, Emberson J, *et al*. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.

13. Kjekshus J, Apetrei E, Barrios V, *et al*, CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248–61.
14. [No authors listed]. Results of the low dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). *Ital Heart J* 2000;1:810–20.
15. Cucherat M, Boissel JP, Leizorovicz A, *et al*. EasyMA: a program for meta-analysis of clinical trials. *Comput Methods Programs Biomed* 1997;53:187–90.
16. Dahl R, Gyrd-Hansen D, Kristiansen IS, *et al*. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey. *BMC Med Inform Decis Mak* 2007;7:8.
17. McConnachie A, Walker A, Robertson M, *et al*. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* 2014;35:290–8.
18. Bulbulia R, Bowman L, Wallendszus K, *et al*, Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet* 2011;378:2013–20.
19. Mihaylova B, Briggs A, Armitage J, *et al*. Heart Protection Study Collaborative. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* 2006;333:1145.
20. Baigent C, Keech A, Kearney PM, *et al*, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78.
21. Holmes HM, Hayley DC, Alexander GC, *et al*. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006;166:605–9.
22. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2998–3007.
23. Sever PS, Dahlof B, Poulter NR, *et al*. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–58.
24. Colhoun HM, Betteridge DJ, Durrington PN, *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–96.
25. Ridker PM, Danielson E, Fonseca FA, *et al*, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
26. Nakamura H, Arakawa K, Itakura H, *et al*, MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006;368:1155–63.
27. Shepherd J, Cobbe SM, Ford I, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–7.
28. [No authors listed]. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
29. Tavazzi L, Maggioni AP, Marchioli R, *et al*, GISSI-HF investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, doubleblind, placebo-controlled trial. *Lancet* 2008;372:1231–9.
30. [No authors listed]. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349–57.