BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007118
Article Type:	Research
Date Submitted by the Author:	21-Nov-2014
Complete List of Authors:	Kristensen, Malene; University of Southern Denmark, Clinical Pharmacology Christensen, Palle; University of Southern Denmark, Clinical Pharmacology Hallas, Jesper; University of Southern Denmark, Clinical Pharmacology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	CLINICAL PHARMACOLOGY, Cardiology < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

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

Malene Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Research unit of Clinical Pharmacology, University of Southern Denmark,
JB Winsløwsvej 19,2, 5000 Odense, Denmark
Malene Lopez Kristensen Cand Pharm
Palle Mark Christensen MD PhD
Jesper Hallas Professor
Department of Clinical Biochemistry and Pharmacology, Odense University Hospital,
Sdr. Boulevard 29, 5000 Odense, Denmark
Jesper Hallas Professor

Correspondence to: Jesper Hallas jhallas@health.sdu.dk

Word count for the review 1.657

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: Six studies were for primary prevention and five for secondary prevention with a follow-up of 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.

Conclusion: Statin treatment results in a surprisingly small average gain in overall survival.

Article summary

Strengths and limitations of this study

• This is the first study ever that systematically evaluates statin trials using average postponement of death as the primary outcome.

• The average postponement of death was surprisingly small. 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.

• 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 focussed on all-cause mortality. Other outcomes may also be relevant, for example non-fatal cardiovascular endpoints.

Introduction

HMG-CoA reductase inhibitors – or "statins" - are important drugs for the prevention in atherosclerotic conditions such as stroke, myocardial infarction or limb ischemia [1]. Current guidelines indicate that statins should be prescribed to all patients with manifest ischemia and to other patients at high risk [1,2], and statins are among the most widely prescribed drugs overall [3].

The magnitude of their preventive effect is controversial, and it is also controversial 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 [6,7] - and to some extent prescribers [8,9] - are not responsive to the NNT-value, i.e. their choices whether to take or to prescribe the drug are largely unaffected by the NNT values given. Also, NNT may be criticized for not being a plausible model for how the benefit of statins is distributed [10]. The thinking behind NNT suggests a lottery-like model, where e.g. 1 in 40 has all the benefit from the drug, and the remaining 39 have no effect. It is more plausible that statins will delay atherosclerotic progression in all treated, to an extent where one in 40 will have his endpoint postponed till after time where the outcome is measured. The remaining 39 also have their endpoints postponed, but none of them to an extent where they cross this time-line. 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 endpoint 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 [4].

To our knowledge, the 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.

Material

Search and inclusion of trials

We based our study on a recent meta-analysis on statins' effect on cardiovascular morbidity or survival, published by Baigent et al [11]. The Baigent paper had retrieved all relevant papers published until end of 2009. We supplemented the Baigent search by using the same search strategy as reported and included the period 2010-2011. Our supplementary literature search yielded one further paper [12].

The included trials in our analysis were defined by being randomised, by having at least 1,000 patients included, by comparing a statin with no treatment or placebo, by having at least two years' follow-up, by having all-cause mortality as a pre-specified primary or secondary endpoint and by providing in the publication a Kaplan-Meier plot of all-cause mortality in treated vs untreated. The eleven included papers are listed in table 1. We have listed the excluded papers in appendix A, also giving the reason for exclusion.

Analysis

An example of the technical aspect of area calculations is shown in Appendix B. In brief, we magnified the Kaplan-Meier graphs from the publications by 300% and imported them into Paint (Microsoft Windows v7). Ten of eleven publications were available in electronically processed format, the last [21] 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-axis

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, CA USA], and the number of pixels between the survival curves was counted by use of 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, where 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, i.e. by drawing triangles by hand on magnified paper prints of the survival curves 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 subjects with known cardiovascular disease prior to randomisation. We calculated summary estimates of odds ratios for all-cause mortality separately for in- and excluded studies by use of standard meta-analysis technique [14].

Results

Out of the 26 publications provided in the original meta-analysis and one retreieved 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 endpoint 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 less than 1 day in seven out of eleven 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 0.84-0.93), compared to 0.91 (CI 0.86-0.96) for the excluded trials.

Discussion

To our knowledge, statin trials have not previously been subjected to a systematic assessment of survival gain by this technique. The survival gains we have found are surprisingly small. The highest value was 27 days found in the 4S study, achieved by 5.8 years of simvastatin therapy in subjects 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 [24].

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 the trials' termination, the treated will continue to accrue survival gain as long as there is 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 [25], and modelling studies have also suggested a large survival benefit with long-term treatment beyond the trials running time [26,27]. 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 and a postponement model could be used [8]. Obviously, this model can be difficult to convey to patients. Third, we have only focussed on all-cause mortality in our analysis. Other outcomes may also be relevant. For example, we have calculated the area between Kaplan-Meier curves for "any cardiovascular endpoint" in the 4S trial, and found an average postponement of 109 days. A systematic postponement analysis of other endpoints than all-cause mortality might thus be warranted. Fourth, we could only include 11 out 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 in- 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. 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 five days from the pixel-count estimates, and most deviations were below one day. Also on a technical note, the standard errors 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 an OR, whose confidence interval crosses the null value. From this study alone, it cannot be ruled out that the intervention is harmful. 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 been developed that incorporates the uncertainty of the net benefit of the drug, such as the confidence interval of the OR, into a postponement model. And there are 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 inexpensive and safe [28], and the benefit in terms of cardiovascular outcomes cannot reasonably be challenged. However, if there are reasons for a patient not to take statins, for example severe muscular complaints, physicians should not be too insistent. Also, for patients whose life-expectancy is short, the benefit of statin therapy in terms of survival gain may be quite limited [29].

Table 1

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

Studie ID	Number included	Intervention/ Comparator	Prevention	Cut-point	Dead: Statin/ control	RR (95 % CI)	NNT	Postponement, days (SD)	Postponement. quick-method (days)
ALLHAT-LLT (2002)	10355	Pravastatin (40mg) vs. usual care	Primary	6 years	14.9 % / 15.3 %	0.99 (0.89-1.11)	250	-4.96 (0.06)	-5.48
ASCOT-LLA (2003)	19342	Atorvastatin (10 mg) vs. placebo	Primary	3.5 years	3.6 % / 4.1 %	0.87 (0.71-1.06)	200	1.99 (0.04)	1.94
CARDS (2004)	2838	Atorvastatin (10 mg) vs. placebo	Primary	4.7 years	4.3 % / 5.8 %	0.73 (0.52-1.01)	66.7	18.66 (0.04)	17.21
JUPITER (2008)	17802	Rosuva-statin (20 mg) vs. Placebo	Primary	2 years	2.22 % / 2.77 %	0.80 (0.67-0.97)	182	1.71 (0.04)	1.85
MEGA (2006)	7832	Pravastatin (5-20 mg) vs. no treatment	Primary	5 years	1.11 % / 1.66 %	0.68 (0.46-1.00)	182	4.42 (0.01)	4.47
WOSCOPS (1995)	6595	Pravastatin (40 mg) vs. Placebo	Primary	5 years	3.2 % / 4.1 %	0.78 (0.60-1.00)	111	9.33 (0.10)	8.29
4S (1994)	4444	Simvastatin (10-40mg) vs. placebo	Secondary	5.8 years	8.7 % / 12.3 %	0.7 (0.58-0.85)	27.8	27.18 (0.26)	31.96
GISSI-HF (2008)	4631	Rosuvastatin (10 mg) vs. placebo	Secondary	4.4 years	28.8 % / 28.1 %	1.00 (0.90-1.12)	-143	-9.51 (0.01)	-10.44
GISSI-P (2000)	4271	Pravastatin (20 mg) vs. no treatment	Secondary	2.0 years	3.37 % / 4.13 %	0.84 (0.61-1.14)	132	1.76 (0.07)	2.53
LIPID (1998)	9014	Pravastatin (40 mg) vs. placebo	Secondary	6.1 years	11.0 % / 14.1 %	0.78 (0.69-0.87)	32.3	22.05 (0.21)	26.59
CORONA (2007)	5011	Rosuvastatin (10 mg) vs. placebo	Secondary	2.7 years	29.0% / 30.4%	0.95 (0.86-1.05)	71	4.09 (0.04)	4.16

SD = Standard deviation

What is already known on this subject

- Statins have been shown to improve overall survival, particularly in secondary prevention trials. How to convey this benefit is controversial
- The average postponement of death can be calculated from the area between the survival curves for treated and untreated in an original trial publication. This effect measure may convey the benefit better than relative risk or number needed to treat.

What this study adds

- The average postponement of death was four weeks or less in secondary prevention trials and three weeks or less in primary prevention trials
- The area between survival curves can be calculated accurately by pixel counting or by trigonometric methods.
- Prescribers should consider the patient's life-expectancy when prescribing statins and should not insist on statin therapy for patients who have adverse effects.

Contributorship
Study concept and design:
Malene Elisa Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Acquisition of data:
Malene Elisa Lopez Kristensen

Analysis and interpretation of data:
Malene Elisa Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Drafting the manuscript:
Malene Elisa Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Critical revision of the manuscript for important intellectual content:
Malene Elisa Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Statistical analysis:
Malene Elisa Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Funding/Support:
Malene Elisa Lopez Kristensen: none
Palle Mark Christensen: none
Jesper Hallas: none

Data sharing
No additional data available.

Competing Interest
None

References

1. Psaty BM, Weiss NS. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol: A Fresh Interpretation of Old Evidence. JAMA 2013 Nov 21. [Epub ahead of print]
2. European Society of Cardiology. European Guidelines on cardiovascular disease prevention in clinical practice version 2012). Eur J Cardiol European Heart Journal 2012; 33: 1635–1701.
3. Simons, John. "The $10 billion pill", Fortune magazine, January 20, 2003.
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: 11S-13S.
7. Christensen PM, Brosen K, Brixen K, Andersen M, Kristiansen IS. 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: 12-6.
11. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. 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.
12. Kjekshus J, Apetrei E, Barrios V, et al, for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357: 2248–61.
13. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–89.
14. EasyMA 2001, Software for meta-analysis of clinical trials. Designed and written by M. Cucherat. Copyright 1992-2001. Department of clinical pharmacology. Cardiological hospital. Lyon - France
15. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. JAMA 2002; 288: 2998–3007.

16. 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.
17. 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.
18. Ridker PM, Danielson E, Fonseca FAH, et al for the 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.
19. Nakamura H, Arakawa K, Itakura H, et al, for the MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006; 368: 1155–63.
20. 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: 1301–07.
21. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). 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? Ital Heart J 2000; 1: 810–20.
22. 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: 1231–39.
23. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–57.
24. Dahl R, Gyrd-Hansen D, Kristiansen IS, Nexøe J, Nielsen JB. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey BMC medical Informatics and Decision Making 2007, 7:8.
25. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. 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 2013 [Epub ahead of print].
26. Støvring H, Harmsen CG, Wisløff T, Jarbøl DE, Nexøe J, Nielsen JB, Kristiansen IS. A competing risk approach for the European Heart SCORE model based on cause-specific and all-cause mortality. Eur J Prev Cardiol 2012 [Epub ahead of print]
27. Heart Protection Study Collaborative, Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. 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.
28. 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.
29. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006 Mar 27;166(6):605-9.
30. 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.
31. 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.
32. 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.
33. 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
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.

40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.

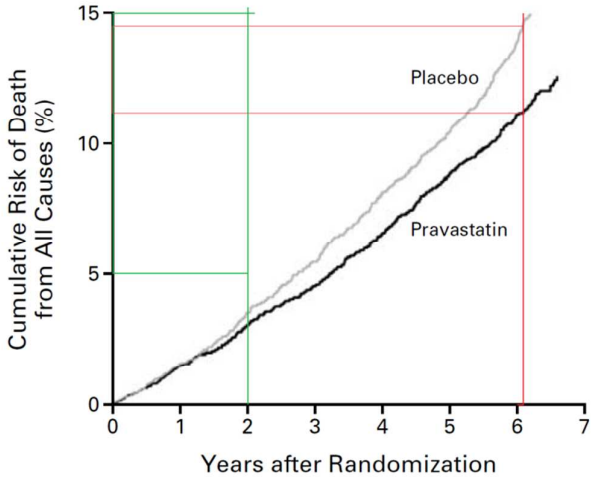
Appendix A

Statin trials excluded from the endpoint postponement analysis

Study ID	Reference	Reason for exclusion
4D (2005)	30	Kaplan-Meier plot on all-cause mortality was not published
AFCAPS/TexCAPS (1998)	31	All-cause mortality was not analyzed
ALERT (2003)	32	Kaplan-Meier plot on all-cause mortality was not published
ALLIANCE (2004)	33	Kaplan-Meier plot on all-cause mortality was not published
ASPEN (2006)	34	Kaplan-Meier plot on all-cause mortality was not published
A – Z (2004)	35	More versus less aggressive statin therapy
AURORA (2009)	36	Kaplan-Meier plot on all-cause mortality was not published
CARE (1996)	37	Kaplan-Meier plot on all-cause mortality was not published
HPS (2002)	38	Kaplan-Meier plot on all-cause mortality was not published
IDEAL (2005)	39	More versus less aggressive statin therapy
LIPS (2002)	40	Kaplan-Meier plot on all-cause mortality was not published
Post – CABG (1997)	41	More versus less aggressive statin therapy
PROSPER (2002)	42	Kaplan-Meier plot on all-cause mortality was not published
PROVE – IT (2004)	43	More versus less aggressive statin therapy
SEARCH (2010)	44	More versus less aggressive statin therapy
TNT (2005)	45	More versus less aggressive statin therapy

Appendix B

Example of calculation of endpoint postponement, LIPID study [23].



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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007118.R1
Article Type:	Research
Date Submitted by the Author:	02-Apr-2015
Complete List of Authors:	Kristensen, Malene; University of Southern Denmark, Clinical Pharmacology Christensen, Palle; University of Southern Denmark, Clinical Pharmacology Hallas, Jesper; University of Southern Denmark, Clinical Pharmacology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	CLINICAL PHARMACOLOGY, Cardiology < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

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

Malene Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Clinical Pharmacology, University of Southern Denmark,
JB Winsløwsvej 19,2, 5000 Odense, Denmark
Malene Lopez Kristensen Cand Pharm
Palle Mark Christensen MD PhD
Jesper Hallas Professor

Department of Clinical Biochemistry and Pharmacology, Odense University Hospital,
Sdr. Boulevard 29, 5000 Odense, Denmark
Jesper Hallas Professor

Correspondence to: Jesper Hallas jhallas@health.sdu.dk

Word count: 2050

Structured 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: Six studies were for primary prevention and five for secondary prevention with a follow- up of 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.

Conclusion: 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 serious adverse effects of treatment, withholding statin therapy should be considered.

Strengths and limitations of this study

- This is the first study ever that systematically evaluates statin trials using average postponement of death as the primary outcome.
- The average postponement of death was surprisingly small. 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.
- 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 focussed on all-cause mortality. Other outcomes may also be relevant, for example non-fatal cardiovascular endpoints.

Introduction

HMG-CoA reductase inhibitors – or "statins" - are important drugs for the prevention in atherosclerotic conditions such as stroke, myocardial infarction or limb ischemia [1]. Current guidelines indicate that statins should be prescribed to all patients with manifest ischemia and to other patients at high risk [1,2], and statins are among the most widely prescribed drugs overall [3].

The magnitude of their preventive effect is controversial, and it is also controversial 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 [6,7] - and to some extent prescribers [8,9] - are not responsive to the NNT-value, i.e. their choices whether to take or to prescribe the drug are largely unaffected by the NNT values given. Also, NNT may be criticized 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 e.g. 1 in 40 has all the benefit from the drug, and the remaining 39 have no effect. It is more plausible that statins will delay atherosclerotic progression in all treated, to an extent where one in 40 will have his endpoint postponed till after time where the outcome is measured. The remaining 39 also have their endpoints postponed, but none of them to an extent where they cross this time-line. 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 endpoint 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 [4].

To our knowledge, the 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.

Material

Search and inclusion of trials

We based our study on a meta-analysis on statins' effect on cardiovascular morbidity or survival, published by Baigent et al [11]. The Baigent paper had retrieved all relevant papers published until end of 2009. We supplemented the Baigent search and included the period 2010-2011. Our supplementary literature search yielded one further paper [12].

The included trials in our analysis were defined by being randomised, by having at least 1,000 patients included, by comparing a statin with no treatment or placebo, by having at least two years' follow-up, by having all-cause mortality as a pre-specified primary or secondary endpoint and by providing in the publication a Kaplan-Meier plot of all-cause mortality in treated vs untreated. The eleven included papers are listed in table 1. We have listed the excluded papers in appendix A, also giving the reason for exclusion.

Analysis

An example of the technical aspects of area calculations is shown in Appendix B. In brief, we magnified the Kaplan-Meier graphs from the publications by 300% and imported them into Paint (Microsoft Windows v7). Ten of eleven publications were available in electronically processed format, the last [13] 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-axis 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, CA USA], and the number of pixels between the survival curves was counted by use of 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, where 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, i.e. 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 subjects with manifest cardiovascular disease prior to randomisation. We calculated summary estimates of odds ratios for all-cause mortality separately for in- and excluded studies by use of standard meta-analysis technique [14].

Results

Out of the 26 publications provided in the original meta-analysis and one retreieved 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 endpoint 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 less than 1 day in seven out of eleven 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 0.84-0.93), compared to 0.91 (CI 0.86-0.96) for the excluded trials.

Discussion

To our knowledge, statin trials have not previously been subjected to a systematic assessment of survival gain by this technique. The survival gains we have found are surprisingly small. The highest value was 27 days found in the 4S study, achieved by 5.8 years of simvastatin therapy in subjects 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 [15].

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 the trials' termination, the treated will continue to accrue survival gain as long as there is 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 [16], but also studies showing that mortality becomes similar in the two groups after the trial's termination [17]. Some modelling studies have

suggested a large survival benefit with long-term treatment beyond the trials running time [18], 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 and a postponement model could be used [8]. This model would convey something similar to "simvastatin resulted in an average of 8 month 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 the patients that has their outcome postponed. In addition, there is very limited experience about how the hybrid model is perceived by patients and how it affects their choices. Third, we have only focussed on all-cause mortality in our analysis. Other outcomes may also be relevant. For example, we have calculated the area between Kaplan-Meier curves for "any cardiovascular endpoint" in the 4S trial, and found an average postponement of 109 days. A systematic postponement analysis of other endpoints than all-cause mortality might thus be warranted. Fourth, we could only include 11 out 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 in- 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 five days from the pixel-count estimates, and most deviations were below one day. Also on a technical note, the standard errors 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 hazard ratio, whose confidence interval crosses the null value. From this study alone, it cannot

be ruled out that the intervention is harmful. 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 been developed that incorporates the uncertainty of the net benefit of the drug, such as the confidence interval of the hazard ratio, into a postponement model. Consequently, there are yet 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 [19], and the benefit in terms of cardiovascular outcomes cannot reasonably be challenged. However, if there are reasons for a patient not to take statins, for example severe muscular complaints, physicians should not be too insistent. Also, for patients whose life-expectancy is short, the benefit of statin therapy in terms of survival gain may be quite limited [20]. Finally, the physician might consider using postponement measures to communicate the benefit to the patients, instead of the NNT or relative risk reductions that are prone to misunderstanding.

Table 1

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

Studie ID, reference, publication yera	Number included	Intervention/ Comparator	Prevention	Cut-point	Dead: Statin/ control	RR (95 % CI)	NNT	Postponement, days (SD)	Postponement. quick-method (days)
ALLHAT-LLT (21) 2002	10355	Pravastatin (40mg) vs. usual care	Primary	6 years	14.9 % / 15.3 %	0.99 (0.89-1.11)	250	-4.96 (0.06)	-5.48
ASCOT-LLA (22) 2003	19342	Atorvastatin (10 mg) vs. placebo	Primary	3.5 years	3.6 % / 4.1 %	0.87 (0.71-1.06)	200	1.99 (0.04)	1.94
CARDS (23) 2004	2838	Atorvastatin (10 mg) vs. placebo	Primary	4.8 years	4.3 % / 5.8 %	0.73 (0.52-1.01)	66.7	18.66 (0.04)	17.21
JUPITER (24) 2008	17802	Rosuva-statin (20 mg) vs. Placebo	Primary	2 years	2.22 % / 2.77 %	0.80 (0.67-0.97)	182	1.71 (0.04)	1.85
MEGA (25) 2006	7832	Pravastatin (5-20 mg) vs. no treatment	Primary	5 years	1.11 % / 1.66 %	0.68 (0.46-1.00)	182	4.42 (0.01)	4.47
WOSCOPS (26) 1995	6595	Pravastatin (40 mg) vs. Placebo	Primary	5 years	3.2 % / 4.1 %	0.78 (0.60-1.00)	111	9.33 (0.10)	8.29
4S (27) 1994	4444	Simvastatin (10-40mg) vs. placebo	Secondary	5.8 years	8.7 % / 12.3 %	0.7 (0.58-0.85)	27.8	27.18 (0.26)	31.96
GISSI-HF (28) 2008	4631	Rosuvastatin (10 mg) vs. placebo	Secondary	4.4 years	28.8 % / 28.1 %	1.00 (0.90-1.12)	-143	-9.51 (0.01)	-10.44
GISSI-P (13) 2000	4271	Pravastatin (20 mg) vs. no treatment	Secondary	2.0 years	3.37 % / 4.13 %	0.84 (0.61-1.14)	132	1.76 (0.07)	2.53
LIPID (29) 1998	9014	Pravastatin (40 mg) vs. placebo	Secondary	6.1 years	11.0 % / 14.1 %	0.78 (0.69-0.87)	32.3	22.05 (0.21)	26.59
CORONA (12) 2007	5011	Rosuvastatin (10 mg) vs. placebo	Secondary	2.7 years	29.0% / 30.4%	0.95 (0.86-1.05)	71	4.09 (0.04)	4.16

SD = Standard deviation

What is already known on this subject

- Statins have been shown to improve overall survival, particularly in secondary prevention trials. How to convey this benefit is controversial
- The average postponement of death can be calculated from the area between the survival curves for treated and untreated in an original trial publication. This effect measure may convey the benefit better than relative risk or number needed to treat.

What this study adds

- The average postponement of death was four weeks or less in secondary prevention trials and three weeks or less in primary prevention trials
- The area between survival curves can be calculated accurately by pixel counting or by trigonometric methods.
- Prescribers should consider the patient's life-expectancy when prescribing statins and should not insist on statin therapy for patients who have adverse effects from it.

Statements

Contributorship statement: Malene Kristensen and Jesper Hallas wrote the first draft of the manuscript. Malene Kristensen performed the analyses and developed the pixel counting method. All authors provided input to the study concept, analysis plan and editing of the manuscript.

Competing interests: Jesper Hallas 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. All others, none declared.

Funding: Funded by University of Southern Denmark.

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

References

1. Psaty BM, Weiss NS. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol: A Fresh Interpretation of Old Evidence. JAMA 2013 Nov 21. [Epub ahead of print]
2. European Society of Cardiology. European Guidelines on cardiovascular disease prevention in clinical practice version 2012). Eur J Cardiol European Heart Journal 2012; 33: 1635–1701.
3. Simons, John. "The $10 billion pill", Fortune magazine, January 20, 2003.
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: 11S-13S.
7. Christensen PM, Brosen K, Brixen K, Andersen M, Kristiansen IS. 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: 12-6.
11. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. 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.
12. Kjekshus J, Apetrei E, Barrios V, et al, for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357: 2248–61.
13. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). 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? Ital Heart J 2000; 1: 810–20.
14. EasyMA 2001, Software for meta-analysis of clinical trials. Designed and written by M. Cucherat. Copyright 1992-2001. Department of clinical pharmacology. Cardiological hospital. Lyon - France

15. Dahl R, Gyrd-Hansen D, Kristiansen IS, Nexøe J, Nielsen JB. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey BMC medical Informatics and Decision Making 2007, 7:8.
16. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. 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 2013 [Epub ahead of print].
17. 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.
18. Heart Protection Study Collaborative, Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. 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.
19. 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.
20. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006 Mar 27;166(6):605-9.
21. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. JAMA 2002; 288: 2998–3007.
22. 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.
23. 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.
24. Ridker PM, Danielson E, Fonseca FAH, et al for the 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.
25. Nakamura H, Arakawa K, Itakura H, et al, for the MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006; 368: 1155–63.
26. 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: 1301–07.

27. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–89.
28. 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: 1231–39.
29. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–57.

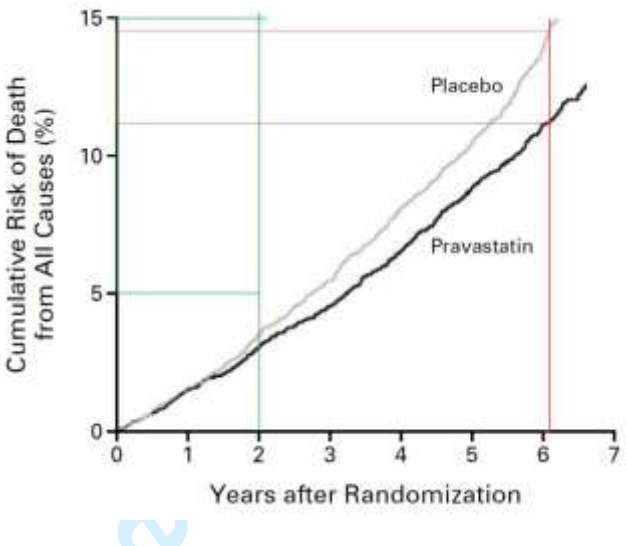
Appendix A

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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007118.R2
Article Type:	Research
Date Submitted by the Author:	29-Apr-2015
Complete List of Authors:	Kristensen, Malene; University of Southern Denmark, Clinical Pharmacology Christensen, Palle; University of Southern Denmark, Clinical Pharmacology Hallas, Jesper; University of Southern Denmark, Clinical Pharmacology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	CLINICAL PHARMACOLOGY, Cardiology < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

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

Malene Lopez Kristensen, Palle Mark Christensen, Jesper Hallas

Clinical Pharmacology, University of Southern Denmark,
JB Winsløwsvej 19,2, 5000 Odense, Denmark
Malene Lopez Kristensen Cand Pharm
Palle Mark Christensen MD PhD
Jesper Hallas Professor

Department of Clinical Biochemistry and Pharmacology, Odense University Hospital,
Sdr. Boulevard 29, 5000 Odense, Denmark
Jesper Hallas Professor

Correspondence to: Jesper Hallas jhallas@health.sdu.dk

Word count: 2050

Structured 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: Six studies were for primary prevention and five for secondary prevention with a follow- up of 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.

Conclusion: 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 that systematically evaluates 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 focussed on all-cause mortality. Other outcomes may also be relevant, for example non-fatal cardiovascular endpoints.

Introduction

HMG-CoA reductase inhibitors – or "statins" - are important drugs for the prevention in atherosclerotic conditions such as stroke, myocardial infarction or limb ischemia [1]. Current guidelines indicate that statins should be prescribed to all patients with manifest ischemia and to other patients at high risk [1,2], and statins are among the most widely prescribed drugs overall [3].

The magnitude of their preventive effect is controversial, and it is also controversial 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 [6,7] - and to some extent prescribers [8,9] - are not responsive to the NNT-value, i.e. their choices whether to take or to prescribe the drug are largely unaffected by the NNT values given. Also, NNT may be criticized 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 e.g. 1 in 40 has all the benefit from the drug, and the remaining 39 have no effect. It is more plausible that statins will delay atherosclerotic progression in all treated, to an extent where one in 40 will have his endpoint postponed till after time where the outcome is measured. The remaining 39 also have their endpoints postponed, but none of them to an extent where they cross this time-line. 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 endpoint 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 our knowledge, the 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.

Material

Search and inclusion of trials

We based our study on a meta-analysis on statins' effect on cardiovascular morbidity or survival, published by Baigent et al [12]. The Baigent paper had retrieved all relevant papers published until 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, by having at least 1,000 patients included, by comparing a statin with no treatment or placebo, by having at least two years' follow-up, by having all-cause mortality as a pre-specified primary or secondary endpoint and by providing in the publication a Kaplan-Meier plot of all-cause mortality in treated vs untreated. The eleven included papers are listed in table 1. We have listed the excluded papers in appendix A, also giving the reason for exclusion.

Analysis

An example of the technical aspects of area calculations is shown in Appendix B. In brief, we magnified the Kaplan-Meier graphs from the publications by 300% and imported them into Paint (Microsoft Windows v7). Ten of eleven 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-axis 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, CA USA], and the number of pixels between the survival curves was counted by use of 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, where 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, i.e. 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 subjects with manifest cardiovascular disease prior to randomisation. We calculated summary estimates of odds ratios for all-cause mortality separately for in- and excluded studies by use of standard meta-analysis technique [15].

Results

Out of the 26 publications provided in the original meta-analysis and one retreieved 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 endpoint 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 less than 1 day in seven out of eleven 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 0.84-0.93), compared to 0.91 (CI 0.86-0.96) for the excluded trials.

Discussion

To our knowledge, statin trials have not previously been subjected to a systematic assessment of survival gain by this technique. The survival gains we have found are surprisingly small. The highest value was 27 days found in the 4S study, achieved by 5.8 years of simvastatin therapy in subjects 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 the trials' termination, the treated will continue to accrue survival gain as long as there is 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 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 trials 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 and a postponement model could be used [8]. This model would convey something similar to "simvastatin resulted in an average of 8 month 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 the patients that has 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 focussed on all-cause mortality in our analysis. Other outcomes may also be relevant. For example, we have calculated the area between Kaplan-Meier curves for "any cardiovascular endpoint" in the 4S trial, and found an average postponement of 109 days. A systematic postponement analysis of other endpoints than all-cause mortality might thus be warranted. Fourth, we could only include 11 out 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 in- 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 five days from the pixel-count estimates, and most deviations were below one day. Also on a technical note, the standard errors 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 hazard ratio, whose confidence interval crosses the null value. From this study alone, it cannot

be ruled out that the intervention is harmful. 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 been developed that incorporates the uncertainty of the net benefit of the drug, such as the confidence interval of the hazard ratio, into a postponement model. Consequently, there are yet 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 towards statins, for example muscular complaints, physicians should not be too insistent that the patient should continue. 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 that 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.

Table 1

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

Studie ID, reference, publication yera	Number included	Intervention/ Comparator	Prevention	Cut-point	Dead: Statin/ control	RR (95 % CI)	NNT	Postponement, days (SD)	Postponement. quick-method (days)
ALLHAT-LLT (22) 2002	10355	Pravastatin (40mg) vs. usual care	Primary	6 years	14.9 % / 15.3 %	0.99 (0.89-1.11)	250	-4.96 (0.06)	-5.48
ASCOT-LLA (23) 2003	19342	Atorvastatin (10 mg) vs. placebo	Primary	3.5 years	3.6 % / 4.1 %	0.87 (0.71-1.06)	200	1.99 (0.04)	1.94
CARDS (24) 2004	2838	Atorvastatin (10 mg) vs. placebo	Primary	4.8 years	4.3 % / 5.8 %	0.73 (0.52-1.01)	66.7	18.66 (0.04)	17.21
JUPITER (25) 2008	17802	Rosuva-statin (20 mg) vs. Placebo	Primary	2 years	2.22 % / 2.77 %	0.80 (0.67-0.97)	182	1.71 (0.04)	1.85
MEGA (26) 2006	7832	Pravastatin (5-20 mg) vs. no treatment	Primary	5 years	1.11 % / 1.66 %	0.68 (0.46-1.00)	182	4.42 (0.01)	4.47
WOSCOPS (27) 1995	6595	Pravastatin (40 mg) vs. Placebo	Primary	5 years	3.2 % / 4.1 %	0.78 (0.60-1.00)	111	9.33 (0.10)	8.29
4S (28) 1994	4444	Simvastatin (10-40mg) vs. placebo	Secondary	5.8 years	8.7 % / 12.3 %	0.7 (0.58-0.85)	27.8	27.18 (0.26)	31.96
GISSI-HF (29) 2008	4631	Rosuvastatin (10 mg) vs. placebo	Secondary	4.4 years	28.8 % / 28.1 %	1.00 (0.90-1.12)	-143	-9.51 (0.01)	-10.44
GISSI-P (14) 2000	4271	Pravastatin (20 mg) vs. no treatment	Secondary	2.0 years	3.37 % / 4.13 %	0.84 (0.61-1.14)	132	1.76 (0.07)	2.53
LIPID (30) 1998	9014	Pravastatin (40 mg) vs. placebo	Secondary	6.1 years	11.0 % / 14.1 %	0.78 (0.69-0.87)	32.3	22.05 (0.21)	26.59
CORONA (13) 2007	5011	Rosuvastatin (10 mg) vs. placebo	Secondary	2.7 years	29.0% / 30.4%	0.95 (0.86-1.05)	71	4.09 (0.04)	4.16

SD = Standard deviation

What is already known on this subject

- Statins have been shown to improve overall survival, particularly in secondary prevention trials. How to convey this benefit is controversial
- The average postponement of death can be calculated from the area between the survival curves for treated and untreated in an original trial publication. This effect measure may convey the benefit better than relative risk or number needed to treat.

What this study adds

- The average postponement of death was in individual trials was in median 3.2 days for primary prevention trials and 4.1 days for secondary prevention trials.
- The area between survival curves can be calculated accurately by pixel counting or by trigonometric methods.
- Prescribers should consider the patient's life-expectancy when prescribing statins and should not insist on statin therapy for patients who have adverse effects from it.

Statements

Contributorship statement: Malene Kristensen and Jesper Hallas wrote the first draft of the manuscript. Malene Kristensen performed the analyses and developed the pixel counting method. All authors provided input to the study concept, analysis plan and editing of the manuscript.

Competing interests: Jesper Hallas 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. All others, none declared.

Funding: Funded by University of Southern Denmark.

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

References

1. Psaty BM, Weiss NS. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol: A Fresh Interpretation of Old Evidence. JAMA 2013 Nov 21. [Epub ahead of print]
2. European Society of Cardiology. European Guidelines on cardiovascular disease prevention in clinical practice version 2012. Eur J Cardiol European Heart Journal 2012; 33: 1635–1701.
3. Simons, John. "The $10 billion pill", Fortune magazine, January 20, 2003.
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: 11S-13S.
7. Christensen PM, Brosen K, Brixen K, Andersen M, Kristiansen IS. 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: 12-6.
11. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions-standardizing data on outcomes. N Engl J Med. 1998 Aug 6;339(6):380–6
12. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. 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, for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357: 2248–61.
14. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). 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? Ital Heart J 2000; 1: 810–20.

15. EasyMA 2001, Software for meta-analysis of clinical trials. Designed and written by M. Cucherat. Copyright 1992-2001. Department of clinical pharmacology. Cardiological hospital. Lyon - France
16. Dahl R, Gyrd-Hansen D, Kristiansen IS, Nexøe J, Nielsen JB. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey BMC medical Informatics and Decision Making 2007, 7:8.
17. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. 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 2013 [Epub ahead of print].
18. 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. Heart Protection Study Collaborative, Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. 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. 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, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006 Mar 27;166(6):605-9.
22. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. 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 FAH, et al for the 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, for the 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: 1301–07.
28. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–89.
29. 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: 1231–39.
30. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–57.

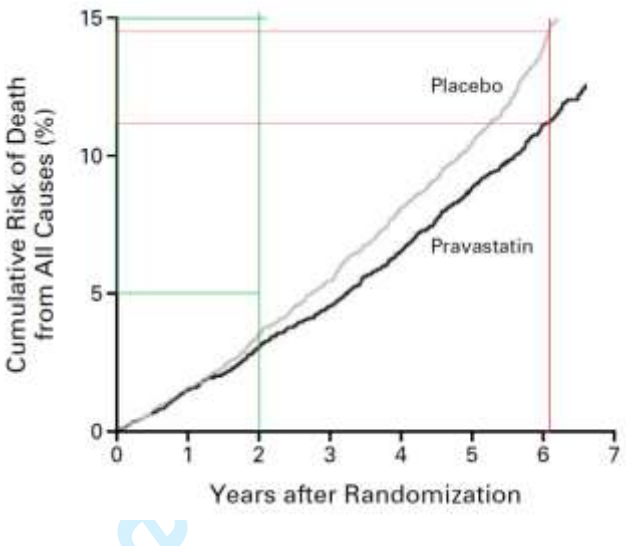
Appendix A

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.