CUMULATIVE IN-TRIAL AND POST-TRIAL EFFECTS OF BLOOD PRESSURE AND LIPID LOWERING: SYSTEMATIC REVIEW AND META-ANALYSIS

Short title: Long-term effects of BP and lipid lowering

Authors:

*Yoichiro Hirakawa[a], *Hisatomi Arima[a,b], Anthony Rodgers[a], Mark Woodward[a,c,d], John Chalmers[a]

*Joint first authors

[a]The George Institute for Global Health, Royal Prince Alfred Hospital and the University of Sydney, Sydney, Australia

[b]Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Japan

[c]The George Institute for Global Health, University of Oxford, Oxford, UK

[d] Department of Epidemiology, Johns Hopkins University, Baltimore, USA

Source of Funding: Supported by Program Grant from the National Health and Medical Research Council of Australia (1052555).

Conflicts of Interest: Dr. Chalmers reports receiving lecture fees and travel support from Servier; Dr. Woodward receiving grant funding from Sanofi and consultancy work for Sanofi and Amgen.

Corresponding Author: Professor John Chalmers, M.D., Ph.D.

The George Institute for Global Health

Royal Prince Alfred Hospital and the University of Sydney

Postal address: PO Box M201, Missenden Road, NSW 2050, AUSTRALIA

Street address: Level 10, KGV building, RPA Hospital, Missenden Road, NSW 2050, AUSTRALIA

Telephone: +61-2-9993-4587

Facsimile: +61-2-9993-4588

Email: chalmers@georgeinstitute.org.au

Word count: 4849 (including references, but not tables and legends)

Abstract: 250 words

Number of tables/figures: 4 figures

Number of supplementary digital content files: 1 (comprising 9 tables, 12 figures and 12 references)

Abstract

Objective: Persistent long-term benefits after discontinuation of treatment have been suggested for blood pressure and lipid lowering treatments. We conducted a systematic review to assess the long-term effects of blood pressure lowering (BPL) and lipid lowering (LL) on all-cause and cardiovascular mortality after discontinuation of randomized treatment.

Methods: We systematically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials. We included large-scale randomized controlled trials of BPL or LL of at least 1 year with post-trial follow-up. We identified 13 BPL trials with 48892 participants and 10 LL trials with 71370 participants. Mean in-trial and post-trial follow-up was approximately 4 and 6 years, respectively.

Results: BP and lipid levels tended to come together soon in the post-trial period. There was significant benefit of BPL on all-cause mortality during the in-trial period (relative risk 0.85, 95% CI 0.81 to 0.89), and significant, but attenuated, benefit during overall follow-up (0.91, 0.87 to 0.94). Likewise, LL with statins reduced the risk of all-cause mortality during the in-trial period (0.88, 0.81 to 0.95), and this effect persisted during overall follow-up (0.92, 0.87 to 0.97). Similar findings were observed for cardiovascular death. In BPL trials, the cumulative reduction in all-cause mortality was significantly lower in trials with ≥5 years of post-trial follow-up compared to those with <5 years, and a similar tendency was observed for LL trials.

Conclusions: Benefits of BPL and LL on all-cause and cardiovascular mortality were persistent, but attenuated, after discontinuation of randomized treatment, indicating the importance of continuing therapy.

Key words: blood pressure lowering, lipid lowering, pos-trial follow-up, meta-analysis, all-cause mortality, cardiovascular mortality.

Abbreviation list

4S, Scandinavian Simvastatin Survival Study; AASK, African-American Study of Kidney Disease and Hypertension; ALERT, Assessment of LEscol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial lipid-lowering trial; ASCOT-LLT, Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm; CI, confidence interval; HDFP, the Hypertension Detection and Follow-up Program; HOPE, the Heart Outcomes Prevention Evaluation; HPS, Heart Protection Study; HYVET, Hypertension in the Very Elderly Trial; LIPID, Ling-term Intervention with Pravastatin Ischaemic Disease; LDLC, low-density lipoprotein cholesterol; PREVEND-IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; Post-CABG, POST Coronary Artery Bypass Graft trial; RR, relative risk; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; SOLVED, the Studies of Left Ventricular Dysfunction; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; UKPDS, the United Kingdom Prospective Diabetes Study; WOSCOPS, West Of SCotland COronary Prevention Study.

Introduction

Cardiovascular disease constitutes one of the leading causes of premature death globally, placing a major burden on the community.[1] Blood pressure lowering and lipid lowering treatments are established cardiovascular prevention strategies, which are broadly applicable across a wide range of blood pressure levels[2-4] or lipid levels.[5-7] Evidence from post-trial follow-up of large scale clinical trials has suggested that these strategies also provide persistent long-term benefits of blood pressure lowering and lipid lowering treatments some years after termination of randomised controlled trials.[8-9] A systematic review of randomized controlled trials demonstrated similar benefits of blood pressure lowering treatment on mortality during in-trial and post-trial periods; however, this systematic review included trials of acute phase of diseases (e.g. acute myocardial infarction) with short duration of treatment.[10] A similar review of post-trial effects of lipid-lowering therapies, conducted by the same group, also reported persistent post-trial benefits after lipid lowering trials using a variety of lipid lowering therapies.[11] However, since the publication of these two meta-analyses, a number of other trial groups have reported on post-trial follow-up of either blood pressure lowering therapy or lipid lowering using statins and accordingly we have conducted an updated meta-analysis of post-trial follow-up of long-term blood pressure lowering, and of cholesterol lowering, specifically using statins.

Unlike the two previous meta-analyses which only compared event numbers in the post-trial period alone, we compared the cumulative number of events from randomization through to the end of post-trial follow-up, which allowed us to maintain the intention-to-treat principle. However we also analyse and report event numbers

in the post-trial period alone, so as to investigate the possibility of post-trial benefits, independently of carry-over effects from the in-trial period.

The aim of the present systematic review and meta-analysis was firstly, to assess the magnitude of long-term benefits of blood pressure lowering drugs and of statins on all-cause and cardiovascular mortality after discontinuation of randomised treatment, and secondly, to assess possible differences between long-term effects seen after trials in different patient populations, or after trials using different drugs, or according to the length of post-trial follow-up.

Methods

Data Sources and Searches

A systematic literature search of randomized clinical trials of blood pressure–lowering therapy and of lipid lowering therapy with statins was performed on 17 March 2015 and on12 May 2015, respectively, using Medline (1946-2015), Embase (1966-2015), and the Cochrane Central Register of Controlled Trials (the Cochrane Library issue 4, 2014) using relevant text words and medical subject headings that included all spellings of antihypertensive agents and statins and post-trial follow-up (see Tables S1 and S2, Supplemental Digital Content 1).

Study Selection

As shown in figure S1 (Supplemental Digital Content 1), 2985 titles were identified for post-trial follow-up studies of clinical trials for blood pressure lowering therapy. Studies were eligible for inclusion if they were extensions of randomized control trials; if they studied effects of a specific blood pressure lowering regimen or a lower

target of blood pressure control; if a comparator was placebo, no treatment or higher target; if sample size was equal to or greater than 1,000 patient-years per randomized group during the in-trial period; if the follow-up period was at least 1 year during both the in-trial and post-trial periods; if the data for either deaths from any cause or from cardiovascular disease were presented for the post-trial period; and if the data for index outcomes were presented for the in-trial period in the original trial of randomized treatment. A total of 46 potentially appropriate post-trial follow-up studies and matching articles for the randomized trial period were reviewed, and 13[3,8,12-35] pairs were finally included (Figure S1 and Table S3, Supplemental Digital Content 1).

We identified 1171 studies with post-trial follow-up of randomized trials using statins. Of these, full articles of 21 pairs of study for both the in-trial and post-trial periods were reviewed, and 10 pairs[6,9,22,23,36-51] met the same criteria as described for blood pressure lowering therapy, and were included in the present analyses (Figure S2 and Table S4, Supplemental Digital Content 1). When several publications for post-trial follow-up were found in full-text for any one trial, that with the longest duration of post-trial follow-up was chosen. SHEP published papers of 14-year follow-up reporting all-cause and cardiovascular death, and of 22-year follow-up reporting all-cause mortality alone. Thus, 22-year paper was used for the analysis of all-cause mortality and 14-year paper was used for that of cardiovascular death.

Data Extraction

Data were extracted according to the type of intervention, type of control, entry criteria, patient characteristics at baseline (age and SBP or LDLC), and treatment effects during in-trial period (difference of decrement in SBP or LDLC between

randomized groups for each trial). Follow-up years, total number of patients and total number of all-cause and cardiovascular deaths were also extracted separately for the in-trial and post-trial periods. The number of patients, and of deaths from any cause or from cardiovascular disease were tabulated separately for the in-trial and post-trial periods, according to randomized treatment (Tables S5 and S6, Supplemental Digital Content 1). Aspects of trial design, including randomization, allocation concealment, comparison of baseline characteristics, blinding, intention-to-treat analysis, and percentage lost to follow-up during in-trial and post-trial periods, were assessed (Table S7, Supplemental Digital Content 1). For the post-trial follow-up period, the difference between randomized groups of the percentage of patients who had taken study medication or relevant drugs as well as of mean values for blood pressure/lipid variables were also summarized.

Data Analysis

The effects of randomized treatment on the cumulative number of events were estimated as relative risks during the in-trial and overall follow-up periods in accord with the intension-to-treat principle. Relative risks and 95% confidence intervals were estimated from a log-binomial model. We determined the relative risk for the in-trial and post-trial periods of each trial using the number of events and the number of patients. Patients who died during the in-trial period were censored for analyses of the post-trial period alone. We also estimated the relative risk of each trial during the overall follow-up period using the number of events and of patients during both the in-trial and the post-trial periods. Data from each trial were pooled using the DerSimonian and Laird random effects model, weighting by inverse variance. The percentage of variability across trials attributable to heterogeneity was estimated

using the i^2 statistic. The potential for publication bias was assessed by Egger's test and presented graphically by constructing funnel plots. Sensitivity analyses were performed to assess how the effect size would shift if possible bias were removed using Duval and Tweedie nonparametric "trim and fill" method.[52] Differences across trials were analyzed according to patient characteristics at baseline (age and SBP or LDLC), to treatment effects observed during the in-trial period (difference of decrement in SBP or LDLC between randomized groups for each trial), and to the number of years of follow-up during the in-trial period alone, during the post-trial period alone and during overall follow-up, using bubble plot and random effects meta-regression analysis. If the values for either of the post-trial follow-up period or the overall follow-up period were not available, these were calculated using the other two values as fully described in the legends to Tables S3 and S4 (Supplemental Digital Content 1). The treatment effects were separately estimated in subgroups defined according to the class of drug used for randomized treatment (trials that used ACE-I for first or second line medications or those that did not, and trials that used pravastatin or other statins), according to the patient's comorbidity (trials where patients with diabetes were enrolled or not), trials that exclusively enrolled patients with heart failure or not, and trials that were conducted exclusively in patients with or without prior myocardial infarction) and according to the length of the post-trial follow-up period (<5 years or ≥5 years). A p-value of less than 0.05 was considered statistically significant for all analyses, which were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and STATA version 13 (Stata, College Station, Texas).

Results

Blood pressure lowering therapies

Eight of the 13 trials of blood pressure lowering therapy used an angiotensin converting enzyme inhibitor as the first or second line medication. Two trials were conducted in patients with diabetes and three trials were conducted in patients with heart failure. In-trial and post-trial follow-up periods ranged from 1 to 8 years and 1 to 18 years, respectively. Mean in-trial and post-trial follow-up was 3.9 and 6.1 years, respectively. Thus, there was considerable heterogeneity among the trials included in these analyses, in terms of study population as revealed in the variations in entry criteria (Table S3, Supplemental Digital Content 1), as well as in study treatment and length of follow-up. In the analysis for all-cause mortality, 48892 patients enrolled during the in-trial period and 40676 patients during the post-trial period. Among them, 5636 and 8787 deaths occurred during the in-trial and post-trial periods, respectively (Table S5, Supplemental Digital Content 1). Among 42468 patients enrolled in the analysis of cardiovascular death during the in-trial period, 3103 patients died of cardiovascular disease. During the post-trial period, 3737 of 31588 patients died of cardiovascular disease.

Overall, among patients who were assigned to the active/intensive treatment, there was significant benefit of blood pressure lowering therapy during the in-trial period (relative risk 0.85, 95% CI 0.81 to 0.89), a much reduced but still statistically significant benefit (p=0.046) during the post-trial period alone (0.95, 0.91 to 1.00), and consequently a significant but attenuated benefit during overall follow-up (0.91, 0.88 to 0.94) (Figures 1 and S3 and Table S5, Supplemental Digital Content 1). Similarly, the risk of cardiovascular death in actively/intensively treated patients was reduced during the in-trial period compared to those in the control group (0.83, 0.78 to 0.89), but not significantly lower during the post-trial period alone (0.93, 0.85 to

1.01). However, the relative risk remained significant but attenuated during overall follow-up (0.88, 0.84 to 0.92).

All but two trials showed favourable effects of blood pressure lowering therapy on death from any cause or from cardiovascular disease during both the in-trial and overall follow-up periods. Despite the differences between the study populations and treatments in these trials, there was no significant heterogeneity in mortality during follow-up across trials (all-cause mortality, I^2= 0% during the in-trial period and 23.5% during overall-follow-up; cardiovascular death, I^2= 0% during the in-trial period and 16.2% during overall follow-up; all p>0.2 for heterogeneity). Funnel plots revealed no evidence of publication bias across trials reviewed in the present analyses (Egger's test, p>0.15 for small study effects: Figure S4, Supplemental Digital Content 1), nor was there any change in the relative risk after imputing potential 'missing studies' using the trim and fill method.

Similar relative risks were observed between ACEI trials and non-ACEI trials, DM trials and non-DM trials, and HF and non-HF trials (all p>0.15 for heterogeneity) (figure 2). However, the relative risk reduction (RRR) of blood pressure lowering therapy during the overall follow-up period was significantly lower in trials with 5 years or more of post-trial follow-up compared to those with less than 5 years of post-trial follow-up. Meta-regression analysis showed 8% decrease in RRR for all-cause death during overall follow-up per 5 years increment in post-trial follow-up (Figure S5, Supplemental Digital Content 1). There were no clear associations of RRR during either in-trial and overall follow-up, with age at baseline, SBP at baseline, difference of delta BP between randomized groups during in-trial period, or duration of in-trial follow-up. (Figures S5 and S6, Supplemental Digital Content 1).

Ten trials reported similar post-trial use of blood pressure lowering medication between the original randomized groups, whereas one trial reported that the proportion given post-trial medication was higher in the actively treated group though the difference in terms of absolute numbers was small. (Table S8, Supplemental Digital Content 1). In 8 of these trials, the differences in mean BP observed during the in-trial period dissipated rapidly in the post-trial period. A sensitivity analysis using these 8 trials alone produced similar results. There were 7 trials that were excluded from the analysis due to the small number of patients but reported the data for the index outcomes. Inclusion of these trials had very little effect on the results presented here (Figures S7 and S8, Supplemental Digital Content 1).

Lipid lowering therapy with statins

There were a variety of different inclusion criteria for these trials, with eight trials including only those with a prior myocardial infarction, and as a result there were differences in event rates across the trials (Table S6, Supplemental Digital Content 1) Five of the 10 trials of lipid-lowering therapy used pravastatin. Follow-up years ranged from 3.2 to 5.4 years during the in-trial period and 2 to 10 years during the post-trial period. On average, in-trial and post-trial follow-up was 4.7 and 5.1 years. ASCOT-LLA included only UK patients during the post-trial period, and ALLHAT-LLT excluded patients from Canadian centers for post-trial follow-up.

The number of patients enrolled was 71370 during the in-trial period and 57799 during the post-trial period in the analysis of all-cause mortality, and 67917 and 54893 in the analysis of cardiovascular death, respectively. Among them, there were 7276, 10671, 3996 and 4856 events, respectively (Table S6, Supplemental Digital Content 1).

Lipid lowering therapy with statins reduced the risk of all-cause mortality during the in-trial period (12%, 5-19%), and this effect persisted during overall follow-up though it was greatly reduced during the post-trial period alone (Figure 3, Figure S9 and Table S6 Supplemental Digital Content 1). Similar effects were observed for cardiovascular mortality. A moderate level of heterogeneity in treatment effects was seen in the statin trials; for all-cause mortality, with I^2 values of 55.0% and p values for heterogeneity of 0.02 during the in-trial period and with 61.4% and 0.01 during overall follow-up; for cardiovascular death, with 43.5% and 0.09 during the in-trial period and with 48.6% and 0.06 during overall follow-up. There was no evidence of publication bias, and relative risks remained unchanged in sensitivity analyses using the trim and fill method (Figure S10, Supplemental Digital Content 1).

Effects of statins were similar between subgroups defined as pravastatin trials versus other statin trials or as trials that included patients with prior myocardial infarction versus trials that excluded them. The sensitivity analysis excluding the trial for renal replacement therapy recipients did not alter the results (pooled relative risk of all-cause mortality: in-trial 0.88, 95% CI 0.81 to 0.95, post-trial 0.97, 0.93-1.02, and overall 0.92, 0.87-0.97). The attenuation of the benefits in mortality during overall follow-up were more marked for trials with more than 5 years of post-trial follow-up though these differences were not significant (figure 4). Meta-regression analyses revealed that high RRR in all-cause mortality during the overall follow-up was associated with high RRR during the in-trial period (Figure S11, Supplemental Digital Content 1). For cardiovascular death, larger differences of LDLC ("delta LDLC") between randomized groups were associated with higher RRR during the in-trial period. Similarly younger age at baseline and longer years of follow-up during the in-trial period were associated with marginal increases in RRR during overall

follow-up (Figure S12, Supplemental Digital Content 1). No other significant associations were observed.

The percentage use of lipid lowering medications during the post-trial period was similar between randomized groups in 7 trials, whilst one trial reported significantly higher use of statins in the active group than in the placebo group although this difference was only small (Table S8, Supplemental Digital Content 1). Six trials reported that the difference in mean values of LDL cholesterol or of total cholesterol during the in-trial period disappeared soon after the end of the post-trial follow-up period. A sensitivity analysis using these 6 trials alone produced similar results to those obtained using all ten trials.

Discussion

The present systematic review and meta-analysis of randomized controlled trials with extended post-trial follow-up demonstrated significant but attenuated reductions in death from any cause and from cardiovascular causes, persisting after the cessation of randomized blood pressure lowering treatment. Similar findings were observed with post-trial follow-up after cessation of randomized lipid lowering treatment. One clear finding was the progressive attenuation of post-trial benefits as the length of post-trial observation increased, particularly for blood pressure lowering trials, though a similar tendency was observed for lipid lowering trials. However, there were no clear differences in the effects of blood pressure or lipid lowering across trials with different types of drugs or those with different patient populations. These data indicate that there are some benefits of BP and LDL lowering that continue after treatment has ceased and risk factor levels have merged.

These results indicate therefore that the retardation of pathological processes as a result of more effective blood pressure lowering or lipid lowering treatment in the actively treated groups during the in-trial period plays some ongoing role in the post-trial period alone. These ongoing benefits are however modest in size and decrease over time, but are nonetheless sufficient to ensure that reductions in mortality are still evident 5 years after treatment has ceased. Thus the benefits at the end of overall follow-up are due to a 10-20% reduction in events during the in-trial period and a 5-10% reduction in the post-trial period. Since the in-trial and post-trial periods were of approximately equal length and observed an approximately equal number of events, the overall benefits for the full duration of follow-up reflect an approximate average of these two effects. Further, there was clearly no evidence of rebound or “catch up” mortality.

As well as the modest reduction in post-trial events, another key finding from the present systematic review is progressive attenuation of benefits with increasing time after the cessation of randomized treatment. These findings indicate that it is important to continue blood pressure and lipid lowering treatments in the long-term in order to provide optimal cardiovascular protection. Indeed it is clear that effective treatment with blood pressure or lipid lowering therapies does not achieve a “cure”. Whether longer treatment periods of randomized treatment would provide longer post-treatment benefits is uncertain, since there are no data of large and long-term risk factor reductions. However, it seems clear that life-long use of risk reducing therapies is essential for patients with high cardiovascular risk.

The strengths of this systematic review and meta-analysis are the rigorous methodology and consistency of the effects across studies. In addition, the effects of randomized treatment are estimated both for overall follow-up, in accord with the intention-to-treat principle, and separately for the in-trial and post-trial periods. The main limitation lies in the considerable heterogeneity among the trials included. This resulted in varying background absolute risk and hence heterogeneity in the absolute effects of randomized treatments, as reflected in Tables S5 and S6 (Supplemental Digital Content 1), which makes pooling of absolute risks inappropriate. There was also limited statistical power to investigate sources of heterogeneity using methods based on tabular data. Further, post-trial phase data on use of medications and differences in blood pressure or lipids between randomized groups were not available for some of the trials. However, similar results were obtained from sensitivity analyses using trials that confirmed the post-trial dissipation of the differences in blood pressure and cholesterol levels between randomized groups.

The benefits of blood pressure lowering and lipid lowering on mortality from any cause or from cardiovascular causes persisted after discontinuation of randomized treatment. However, the magnitude of post-trial benefits progressively attenuated with increasing length of post-trial follow-up. These findings suggest that both early and continuing pharmacological treatment using blood pressure and lipid lowering medications are essential for optimal prevention of premature death from any cause or from cardiovascular causes.

Acknowledgement

Source of Funding: Supported by a Program Grant from the National Health and Medical Research Council of Australia (1052555).

Conflicts of Interest: Dr. Chalmers reports receiving lecture fees and travel support from Servier; Dr. Woodward receiving grant funding from Sanofi and consultancy work for Sanofi and Amgen.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.

2. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.

3. Patel A, MacMahon S, Chalmers J,et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829-40.

4. Czernichow S, Zanchetti A, Turnbull F,et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens 2011;29:4-16.

5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.

6. 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.

7. 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.

8. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392-406.
9. 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.
10. Kostis WJ, Thijs L, Richart T, Kostis JB, Staessen JA. Persistence of mortality reduction after the end of randomized therapy in clinical trials of blood pressure-lowering medications. Hypertension 2010;56:1060-108.
11. Kostis WJ, Moreyra AE, Cheng JQ, Dobrzynski JM, Kostis JB. Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy. J Clin Lipidol 2011;5:97-104.
12. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31.
13. Appel LJ, Wright JT Jr, Greene T, et al. N Engl J Med 2010;363:918-29.
14. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. II. Mortality by race-sex and age. JAMA 1979;242:2572-7.
15. Hypertension Detection and Follow-up Program Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. JAMA 1988;259:2113-22.
16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.

17. Bosch J, Lonn E, Pogue J, et al. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation 2005;112:1339-46.
18. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98.
19. Beckett N, Peters R, Tuomilehto J, et al. Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. BMJ 2011;344:d7541.
20. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801-7.
21. Pedersen TR. Six-year follow-up of the Norwegian Multicenter Study on Timolol after Acute Myocardial Infarction. N Engl J Med 1985;313:1055-8.
22. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110:2809-16.
23. Brouwers FP, Asselbergs FW, Hillege HL, et al. Long-term effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria:Ten years of follow-up of Prevention of Renal and Vascular End-stage Disease Intervention Trial (PREVEND IT). Am Heart J 2011;161:1171-8.
24. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.

25. Patel AB, Kostis JB, Wilson AC, Shea ML, Pressel SL, Davis BR. Long-term fatal outcomes in subjects with stroke or transient ischemic attack: fourteen-year follow-up of the systolic hypertension in the elderly program. Stroke 2008;39:1084-9.
26. Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, Davis BR. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 2011;306:2588-93.
27. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
28. The SOLVD Investigattors. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-91.
29. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003;361:1843-8.
30. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757-64.
31. Staessen JA, Thijisq L, Fagard R,et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J Hypertens 2004;22:847-57.
32. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670-6.

33. Buch P, Rasmussen S, Abildstrom SZ, et al. The long-term impact of the angiotensin-converting enzyme inhibitor trandolapril on mortality and hospital admissions in patients with left ventricular dysfunction after a myocardial infarction: follow-up to 12 years. Eur Heart J 2005;26:145-52.
34. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
35. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359:1565-76.
36. Scandinavian Simvastatin Survival Study Froup. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
37. Strandberg TE, Pyörälä K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004;364:771-7.
38. Holdaas H, Fellström 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.
39. Holdaas H, Fellström B, Cole E, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant 2005;5:2929-36.
40. 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.
41. Margolis KL, Davis BR, Baimbridge C,et al. Long-term follow-up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J Clin Hypertens. 2013;15:542-54.
42. Sever PS, Dahlöf 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.
43. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. Eur Heart J 2011;32:2525-32.
44. 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.
45. LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet 2002;359:1379-87.
46. Shepherd J, Blauw GJ, Murphy MB, et al. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-30.

47. Lloyd SM, Stott DJ, de Craen AJ, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One 2013;8:e72642.
48. 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.
49. Knatterud GL, Rosenberg Y, Campeau L, et al. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Post CABG Investigators. Circulation 2000;102:157-65.
50. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301-7.
51. Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med 2007;357:1477-86.
52. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

Figure legends

Figure 1. Forest plot for all-cause mortality and cardiovascular death during the in-trial period and during overall follow-up of the trials of blood pressure lowering therapy reviewed in these analyses

AASK, African-American Study of Kidney Disease and Hypertension; HDFP, the Hypertension Detection and Follow-up Program; HOPE, the Heart Outcomes Prevention Evaluation; HYVET, Hypertension in the Very Elderly Trial; PREVEND IT, Prevention of Renal and Vascular End-stage Disease Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; SOLVED, the Studies of Left Ventricular Dysfunction; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; UKPDS, the United Kingdom Prospective Diabetes Study; RR, relative risk; CI, confidence interval.

Solid squares represent the relative risks for individual trials and have a size proportional to the inverse of the variance. Diamonds denote summary statistics. Horizontal lines and transverse diagonal length of diamonds denote 95% CIs. Pooled RRs were estimated using random effect models.

Figure 2. Pooled estimates for all-cause and cardiovascular death observed in reviewed trials of blood pressure lowering therapy by subgroups of drug class, patients profile and duration of post-trial follow-up period

'ACE-I trials' denotes trials that used ACE-I for first or second line medications. 'DM trials' denotes trials where only patients with diabetes were enrolled. 'Non-DM trials' denotes trials that were not exclusively conducted in DM patients, but could include patients with DM. 'HF trials' denotes trials where only patients with heart failure were included, whereas 'Non-HF trials' denotes trials that were not exclusively conducted in patients with heart failure. For further explanation, please see Figure 1.

Figure 3. Forest plot for all-cause mortality and cardiovascular death during the in-trial period and during overall follow-up of the reviewed trials of lipid lowering therapy

4S, Scandinavian Simvastatin Survival Study; ALERT, Assessment of LEscol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial lipid-lowering trial; ASCOT-LLT, Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm; HPS, Heart Protection Study; LIPID, Ling-term Intervention with Pravastatin Ischaemic Disease; PREVEND-IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; Post-CABG, POST Coronary Artery Bypass Graft trial; WOSCOPS, West Of SCotland COronary Prevention Study; RR, relative risk; CI, confidence interval.

Solid squares represent the relative risks for individual trials and have a size proportional to the inverse of the variance. Diamonds denotes summary statistics. Horizontal lines and transverse diagonal length of diamonds denote 95% CIs. Pooled RRs were estimated using random effect models.

Figure 4. Pooled estimates for all-cause and cardiovascular death observed in reviewed trials of lipid lowering therapy by subgroups of drug class, patients profile and duration of post-trial follow-up period.

Statins were categorised ‘pravastatin water soluble’ or ‘others lipid soluble’. Trials were categorized as ‘including prior MI’ when they included patients with prior MI or as ‘excluding prior MI’ when they were exclusively conducted in patients without prior MI. For further explanation, please see Figure 3.

List of Supplemental Digital Content

Supplemental Digital Content 1. Supplementary tables and figures. docx