Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaboration*

Correspondence to CTT Secretariat:

National Health and Medical Research Council (NHMRC) Clinical Trials Centre

Level 6 Medical Foundation Building

92-94 Parramatta Rd, Camperdown, NSW 2050, Australia

Email: ctt@ctc.usyd.edu.au

Phone: +61 2 9562 5000

Fax: +61 2 9562 5090

or

Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU)

Richard Doll Building, Old Road Campus,

Roosevelt Drive, Oxford OX3 7LF, UK

Email: ctt@ctsu.ox.ac.uk

Phone: +44 1865 743743

Fax: +44 1865 743985

09 December 2015

* Collaborators are listed at the end of the report

Summary

Background

There has been debate about whether statin therapy is as effective in women as men, especially for primary prevention.

Methods

Meta-analyses were performed on data from 22 trials of statin therapy vs. control (n=134 537) and five trials of more intensive vs. less intensive statin therapy (n=39 612). Effects on major vascular events, major coronary events, stroke, coronary revascularisation and mortality were weighted per 1·0 mmol/L reduction in LDL cholesterol and effects in men and women compared using a Cox model that adjusted for non-gender differences. For subgroup analyses, 99% confidence intervals were used to make allowance for the multiplicity of comparisons.

Findings

Overall, 46675 (27%) of 174,149 randomised participants were women. Allocation to a statin had similar absolute effects on 1-year lipid concentrations in both men and women (LDL cholesterol reduced by ~1·1mmol/L in statin vs. control trials and ~0·5mmol/L in more vs. less trials). The proportional reductions per 1·0 mmol/L reduction in LDL cholesterol in major vascular events were similar in women (RR 0·84, 99% CI 0·78-0·91) and men (RR 0·78, 99% CI 0·75-0·81), both overall (adjusted p value for heterogeneity by gender=0·33) and among those at <10% predicted 5-year risk (adjusted heterogeneity p=0·11). Likewise, the proportional reductions in major coronary events, coronary revascularisation and stroke did not differ by gender. Since there were similar proportional reductions in vascular mortality in women (RR 0·92, 99% CI 0·82-1·03) and men (RR 0·87, 99% CI 0·82-0·92) (adjusted heterogeneity p=0·84), but no apparent effect on non-vascular deaths in either sex, all-cause mortality was reduced in both women (RR 0·91, 99% CI 0·84-0·99) and men (RR 0·90, 99% CI 0·86-0·95).

Interpretation

Other things being equal, statin therapy is of comparable effectiveness for the prevention of major vascular events in women as in men, even among those at low risk of vascular disease.

Funding

UK Medical Research Council, British Heart Foundation, Australian National Health and Medical Research Council, European Community Biomed Program.

Introduction

There is general agreement that statins reduce both cardiovascular events and mortality,[1-4] but uncertainty remains regarding the extent of their efficacy in women compared with men,[5] especially for primary prevention.[5-11] Few studies have reported independently significant cardiovascular benefits in women,[5, 12-15] and much of the resulting uncertainty has been attributed to the under-representation of women in statin trials, and a lack of gender-specific analyses in cardiovascular research.[16, 17]

Previous meta-analyses of the effects of statin therapy in women have reached conflicting conclusions. A meta-analysis in 2010 concluded that, among individuals without known cardiovascular disease, statins may not be as effective in women as in men,[10] whereas a more recent meta-analysis in 2012 (that included mainly primary, but some secondary prevention patients) concluded statins are effective in both sexes.[15] Both studies, however, were only able to access information from a subset of the relevant trials and utilised published data, thereby limiting the reliability of their findings. Perhaps as a result of this uncertainty, a recent review concluded that there is a need for a large trial of statin therapy among women.[11]

The Cholesterol Treatment Trialists' (CTT) Collaboration previously reported meta-analyses of individual data from 22 trials of standard statin regimens versus control and 5 trials of more intensive vs less intensive regimens in which it was shown that the proportional benefits of statin therapy on major vascular events are similar irrespective of baseline risk of vascular disease.[4] In that study, a subsidiary analysis indicated that the proportional effects of statins on major vascular events did not differ in women and men of equivalent baseline risk of vascular disease. The purpose of the current report is to provide a more detailed assessment of the effects of statin therapy on particular vascular and non-vascular outcomes in men and women in both primary and secondary prevention settings.

Methods

Study Design

A protocol for the Cholesterol Treatment Trialists' (CTT) Collaboration was agreed in November 1994, before the results of any of the relevant trials became available.[18] Randomised trials were

eligible for inclusion if: (i) the main effect of at least one of the trial interventions was to lower LDL cholesterol; (ii) the trial was unconfounded with respect to this intervention (ie, no other differences in modification of risk factors between the relevant treatment groups were intended); and (iii) the trial aimed to recruit 1000 or more participants with treatment duration of at least 2 years. The outcomes recorded were major vascular events, major coronary events (defined as non-fatal myocardial infarction (MI) or coronary death), coronary revascularisation (angioplasty or bypass grafting), stroke (subdivided by type), site-specific cancers and cause specific mortality.

Statistical Analysis

Separately for women and men, the absolute difference in one year lipid concentrations between those participants allocated active treatment (statin therapy or more intensive statin therapy) and those allocated control (no statin, usual care or less intensive statin therapy) was calculated as a weighted average of the lipid differences across the trials, weighted by the trial and sex-specific variances of the observed log-rank (o-e) for major vascular events. Standard errors were calculated from the variances of the components of the differences using the standard formula for the variance of a linear combination with the weights treated as fixed constants.[19] Estimates of the mean effect on lipid concentrations were compared between women and men using a t-test.

The meta-analysis was conducted according to the intention-to-treat principle. In each trial the effects on disease event rates were derived from the log-rank statistic (o-e) and its variance (v) for each first event and weighted by the absolute difference in LDL cholesterol (d mmol/L) after 1 year between active treatment and control for that trial. Trial results were combined using the log of the rate ratio per mmol/L (log RR) calculated as S/V with variance $1/V$ (and hence with 95% CI of $S/V \pm 1.96/\sqrt{V}$), where S is the sum over all trials of $d(o\text{-}e)$ and V is the sum over all trials of d^2v. For most subgroup analyses, the weight used for a particular subgroup was the LDL cholesterol difference observed in the whole trial, but analyses by baseline LDL cholesterol concentration used trial- and subgroup- specific LDL cholesterol weightings. In trials comparing more versus less intensive statin therapy, baseline lipid values would be those achieved on the less intensive regimen. However in three of these trials,[20-22] statin therapy was stopped before randomisation. Therefore, for these trials, baseline values on the less intensive regiment were corrected by multiplying the values at the randomisation visit (ie. off statin treatment) by the mean proportional reduction observed at one year among those allocated the less intensive regimen. Results are presented as one-step estimates of the average event rate ratio, representing the effect of treatment per 1·0 mmol/L reduction in LDL cholesterol.

In order to ensure that the effects of allocation to statin therapy were assessed among women and men at similar baseline risk of vascular disease, we used Cox proportional hazards models (as previously described[4]) to categorise women and men in trials of statin versus control (22 trials; model 1) and trials of more versus less intensive statin regimens (five trials; model 2) into one of four baseline categories of 5-year risk of a major vascular event: <10%; ≥10% to <20%; ≥20% to <30%; or ≥30%. The models for both comparisons incorporated terms derived from characteristics measured at the time of randomisation, terms that modelled average differences in risk between trials (as well as within specific periods of time within each trial), and interaction terms. Further details of model development are shown in the appendix pp 12-14.

Statistical tests for heterogeneity of treatment effects in women and men were performed using both standard and adjusted χ^2 tests to take account of important non-gender differences between women and men. Adjusted χ^2 tests were estimated using a Cox proportional hazards regression model, stratified by trial, that included age, diabetes, smoking, hypertension, history of vascular disease (defined as known coronary heart disease, cerebrovascular disease, or peripheral vascular disease), a treatment allocation variable weighted by one-year LDL reduction and an interaction term between gender and that weighted treatment allocation variable (for further details of the model see appendix pp 12-14).

To allow for multiple subdivision of the data into subgroups, only summary rate ratios are presented with 95% CIs; all other rate ratios are presented with 99% CIs. All analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Role of the funding source

No funding source had any role in study design, data collection, data analysis, data interpretation or writing of this manuscript. The writing committee had full access to all the data in the study and take final responsibility for its content.

Results

Individual participant data were available from 27 trials of statin therapy, 22 trials examining statin therapy vs. control and five trials examining more intensive statin therapy vs. less intensive therapy (Table 1).[2, 23] Overall, the median duration of follow up among survivors was 4·9 years (range 2·0

years[20, 24, 25] to 7·0 years[26]). Among all trials, 46675 (27%) of 174149 randomised participants were women. Compared to men, women were older (mean age 65·1 vs 61·8 years) and had a higher prevalence of hypertension (60·0% vs. 47·5%) and diabetes mellitus (23·6% vs. 17·8%), but were less likely to smoke (16·3% vs 20·4%) or have a history of vascular disease (46·6% vs. 64·6%; table 2). In each group of trials, baseline mean total and LDL cholesterol concentrations were similar in women and men (table 2 & webfigure 1). All baseline characteristics examined were statistically significantly different between men and women (P<0·0001).

Combining the two trial types (statin vs. control and more vs. less), statin or more intensive-dose therapy (statin/more) reduced total cholesterol, LDL cholesterol and triglyceride concentrations compared to control or less intensive-dose therapy (control/less) from baseline to year one in both sexes by similar absolute amounts (webfigure 1).

Among all 27 trials, statins reduced the risk of major vascular events by 21% per 1·0 mmol/L LDL cholesterol reduction (RR 0·79, 95% CI 0·77-0·81; p<0·0001), with significant reductions in both women and men. After adjusting for non-gender differences in baseline prognostic characteristics, there was no evidence that the proportional effects of statins in women (RR 0·84, 99% CI 0·78-0·91; p<0·0001) and men (RR 0·78, 99% CI 0·75-0·81; p<0·0001) differed (heterogeneity unadjusted p=0·021, adjusted p=0·331; figure 1). Among the 22 trials of statin vs control, the proportional reductions in major vascular events per 1·0 mmol/L reduction in LDL cholesterol appeared slightly smaller among women than men (heterogeneity unadjusted p=0·023, adjusted p=0·051; webfigure 2), but they were highly significant (p<0·0001) in both women (RR 0·85, 99% CI 0·78-0·92) and men (RR 0·78, 99% CI 0·75-0·82). Among trials of more vs less intensive therapy, the proportional reductions were similar in women and men (unadjusted p=0·623, adjusted p=0·570; webfigure2).

The proportional reductions in major vascular events were also similar among those with a definite history of vascular disease (heterogeneity unadjusted p=0·098, adjusted p=0·431; figure 1), whilst effects amongst those with no known history of vascular disease appeared slightly greater in men (HR 0·72, 99% CI 0·66-0·80) than women (HR 0·85, 99% CI 0·72-1·00) (heterogeneity unadjusted p=0·033, adjusted p=0·023; figure 1). The category of people without a history of vascular disease included, however, some individuals with high vascular risk comorbidities such as renal disease or diabetes, so does not necessarily represent a 'healthy' population. Using the model-derived estimated risk of major vascular events (see webappendix) to categorise each trial participant, the proportional reductions in major vascular events were still found to be broadly similar irrespective of

gender at all levels of risk, including those with 5-year risk <10% (heterogeneity p=NS (unadjusted and adjusted) for all risk categories except risk group ≥10 to <20% (unadjusted heterogeneity p=0·021, adjusted p=0·027); figure 2). The proportional reductions in major vascular events were similar among women and men in each year of treatment (webfigure 3), and also did not appear to differ at different levels of baseline LDL cholesterol concentration (heterogeneity p=NS (unadjusted and adjusted); webfigure 4).

Among all 27 trials, statins reduced the risk of major coronary events by 24% per 1·0 mmol/L LDL cholesterol reduction (RR 0·76, 95% CI 0·73-0·79, p<0·0001), with significant reductions in both women (RR 0·83, 99% CI 0·74-0·93, p<0·0001) and men RR 0·74, 99% CI 0·70-0·78, p<0·0001) (figure 3). As for major vascular events, these reductions were broadly similar irrespective of gender at all levels of risk, including those with 5-year risk of major vascular events <10% ($\chi 2$ tests for heterogeneity p=NS (adjusted and unadjusted); webfigure 5). Statin therapy also reduced coronary revascularisation procedures by 24% per 1·0 mmol/L LDL cholesterol reduction (RR 0·76, 95% CI 0·73-0·78), again with no evidence of a gender difference at different levels of risk (heterogeneity p=NS (unadjusted and adjusted); figure 3 & webfigure 6). The subtype-specific proportional effects of statin therapy were similar in women and men for ischaemic stroke, haemorrhagic stroke and stroke of unknown aetiology (webfigure 7), so that the overall proportional reduction of 15% per 1·0 mmol/L LDL cholesterol reduction in any stroke (RR 0·85, 95% CI 0·80-0·89) was also similar in women and men (heterogeneity p=NS (unadjusted and adjusted); figure 3). Likewise, the proportional effects of statin therapy on both ischaemic stroke (webfigure 8) and any stroke (webfigure 9) were broadly similar (heterogeneity p=NS (unadjusted and adjusted)) irrespective of gender at all levels of risk.

Overall, statin therapy produced a highly significant 12% proportional reduction in vascular mortality (RR 0·88, 95% CI 0·84-0·91) per 1·0 mmol/L LDL cholesterol reduction and a nominally significant reduction in deaths from unknown cause (RR 0·87, 95%CI 0·77-0·99), but had no significant effect on deaths from non-vascular causes (RR 0·96, 95% CI 0·92-1·02), producing an all-cause mortality reduction of 9% per 1·0 mmol/L LDL cholesterol reduction (RR 0·91, 95% CI 0·88-0·93; figure 4). After adjusting for non-gender differences, there was no evidence that the proportional effects differed between women and men for any of these categories of causes of death: consequently there were similar proportional reductions in all-cause mortality per 1·0 mmol/L LDL cholesterol reduction of 10% in men (RR 0·90, 99% CI 0·86-0·95) and 9% in women (RR 0·91, 0·84-0·99, heterogeneity unadjusted p=0·804, adjusted p=0·432; figure 4).

There was no significant effect on any incident cancer or on cancer mortality, and no evidence that statin therapy had different effects in women and men (heterogeneity p=NS (unadjusted and adjusted); webfigure 10).

Discussion

This analysis of individual patient data from over 174000 people represents the largest meta-analysis performed to date comparing statin efficacy by sex and is the only such analysis to adjust in detail for cardiovascular risk. It is widely accepted that reducing LDL cholesterol with statin therapy reduces the risk of major coronary events, coronary revascularisation and ischaemic stroke, and that the absolute benefits of statin therapy are determined chiefly by the absolute magnitude of the LDL cholesterol reduction and the underlying risk of vascular disease in the population treated.[4] There has, however, been uncertainty about whether statin therapy is as effective in women as it is in men[5, 27] especially for primary prevention.[5-11, 28, 29]

The controversy over whether women benefit to the same extent as men from statin therapy is largely attributable to a relative lack of information on the effects in women from individual trials. Only three constituent trials in this meta-analysis had independently significant reductions for women in major vascular events and none reported a mortality reduction. Cardiovascular clinical trials have generally recruited far fewer women than men,[30] at least in part because women develop coronary heart disease an average of 10 years later than men and trials often excluded older individuals. This has resulted in a relative lack of statistical precision in estimates of treatment effects among women.

A major limitation of previous meta-analyses of published trial data is that they could provide only crude comparisons that did not take into account non-gender differences among women and men recruited into individual trials. [5, 9, 10, 15, 31] For this reason, they have had limited capacity to help guide determinations about whether, for an individual at a given level of vascular risk, the proportional and absolute effects of statin therapy might depend on gender. Using individual participant data, the present analyses of the Cholesterol Treatment Trialists' (CTT) Collaboration database have been able to demonstrate conclusively that among women and men at comparable risk of major vascular events, the proportional and absolute effects of statin therapy on major vascular events and mortality are similar. This is true not only among high-risk populations with established

cardiovascular disease, but also when statin therapy is used for the primary prevention of major vascular events in low risk populations.

These results indicate that for each 1 mmol/L reduction in LDL cholesterol, statin therapy reduced major vascular events by about one fifth, major coronary events by one quarter, coronary revascularisations by one quarter and ischaemic stroke by just under one fifth, and that these proportional reductions were similar in men and women. Any apparent differences between genders in the magnitude of proportional reductions achieved with statin therapy could in most instances be explained largely by differences in baseline characteristics between men and women. There were also comparable proportional reductions in vascular causes of death in both sexes which, in the absence of clear differences in other causes of death, produced a 9% per mmol/L LDL cholesterol reduction in all-cause mortality in both sexes. Whereas previous meta-analyses of primary prevention looking specifically at cardiovascular benefits in women have reached conflicting conclusions,[10, 15] we are now able to provide reliable estimates of the effects of statin therapy for the primary prevention of major vascular events in both sexes. Among individuals with no definite history of major vascular events, there were statistically significant proportional reductions in both women and men. Since this category included some participants with high vascular risk comorbidities such as heart failure or renal failure, we determined that even among those who had an estimated 5 year risk of major vascular events of <10%, for each 1 mmol/L reduction in LDL cholesterol, statin therapy significantly reduced the risk of major vascular events by 35% in men and 26% in women.

Existing European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidaemias recommend that statin therapy is used in most individuals with a 10 year risk of *fatal* cardiovascular disease ≥5% and should be considered in those at a moderate risk (≥1 to <5%), depending on LDL cholesterol levels.[32] New guidelines from the National Institute for Health and Care Excellence (NICE) recommend statin therapy for primary prevention in people with a predicted 10 year risk of a cardiovascular event (defined as angina, myocardial infarction, stroke or transient ischaemic attack) of at least 10%.[33, 34] Similarly, the most recent (2013) American College of Cardiology/American Heart Association Blood Cholesterol guidelines advocate statin therapy, largely irrespective of baseline LDL cholesterol, according to an absolute 10 year risk of atherosclerotic cardiovascular disease (defined as nonfatal myocardial infarction, coronary death, nonfatal or fatal stroke) ≥7·5% in both men and women aged between 40-75.[35] The broadly similar proportional (and hence absolute) effects of statin therapy in men and women at similar risk provide reassurance that

such ‘risk-based’ guidelines can be applied similarly to both genders: the absolute numbers of major vascular events that will be avoided for every 1000 participants at 5 year risk of <10% for each 1·0 mmol/L reduction in LDL cholesterol is 12 in men vs 9 in women.

As previously documented these benefits greatly outweigh the known hazards, even among those at lowest risk of major vascular events.[4] Clinical myopathy carries an excess incidence of about 0.5 per 1000 statin treated patients over five years, with an excess incidence of rhabdomyolysis of 0.1 per 1000 over five years.[36] By comparison statin therapy prevented 43 major vascular events per 1000 treated over five years among this overall population and 11 per 1000 treated in those with a 5 year risk of <10%. Myalgia rates are not currently available in the CTTC database. The risk of incident diabetes with statin therapy has been estimated to increase by about 10%.[37, 38] Even amongst those patients with a five year vascular risk under 10%, the cardiovascular risk from such a diagnosis occurring with statin therapy is estimated to be fifty times smaller than the benefits.[4] The present results show that these net benefits are also independent of gender.

Conclusions

Irrespective of gender, statins reduce cardiovascular events and all-cause mortality. Benefits greatly exceed known hazards, even among those at low absolute cardiovascular risk. In view of the substantial burden of cardiovascular disease in both developed and developing countries, and the widespread availability of generic statins, these results indicate they are an effective means of preventing such disease among women as well as men.

Contributors

The writing committee accepts full responsibility for the content of this paper. All of the members contributed to collection and analysis of the data. Conceived and designed the experiments: AK JF AKI JS CB JE RC. Acquisition of data: CB JE RC AK AKI JS. Analysed the data: JF AK ROC MV AKI JE LB. Wrote the paper: JF* AK* CB* ROC JE LB. Critical revision of manuscript for important intellectual content: JF* ROC MV JE LB JS RC AKI HC EB JLR TP AT BD PS MGF CB* AK*. All collaborators had an opportunity to contribute to the interpretation of the results and to drafting of the report.

*These authors contributed equally

Current membership of the CTT Collaboration

Writing Committee

Jordan Fulcher*, Rachel O'Connell, Merryn Voysey, Jonathan Emberson, Lisa Blackwell, John Simes, Rory Collins, Adrienne Kirby, Helen Colhoun, Eugene Braunwald, John La Rosa, T.R.Pedersen, Andrew Tonkin, Barry Davis, Peter Sleight, Maria Grazia Franzosi, Colin Baigent*, Anthony Keech*

*These authors contributed equally to this manuscript

Collaborating trialists

A to Z trial (phase Z) J de Lemos, E Braunwald, M Blazing, S Murphy; AFCAPS/TEXCAPS (AirForce/Texas Coronary Atherosclerosis Prevention Study) J R Downs, A Gotto, M Clearfield; ALERT (Assessment of Lescol in Transplantation) H Holdaas; ALLHAT (Antihypertensive Lipid Lowering Heart Attack Trial) D Gordon, B Davis; ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events) M Koren; ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) B Dahlof, N Poulter, P Sever; ASPEN (Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin Dependent Diabetes Mellitus) R H Knopp (deceased); AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events) B Fellström, H Holdaas, A Jardine, R Schmieder, F Zannad; BIP (Bezafibrate Infarction Prevention Study) U Goldbourt, E Kaplinsky; CARDS (Collaborative Atorvastatin Diabetes Study) H M Colhoun, D J Betteridge, P N Durrington, G A Hitman, J Fuller, A Neil; 4D (Die Deutsche Diabetes Dialyse Studie) C Wanner, V Krane; CARE (Cholesterol And Recurrent Events Study) F Sacks, L Moyé, M Pfeffer; C M Hawkins, E

Braunwald; CORONA (Rosuvastatin in Older Patients with Systolic Heart Failure) J Kjekshus, H Wedel, J Wikstrand; FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) P Barter, A Keech; GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)–Heart Failure L Tavazzi, A Maggioni; GISSI–Prevention R Marchioli, G Tognoni, M G Franzosi, A Maggioni; HIT (Veteran Administration Low HDL Intervention Trial) H Bloomfield, S Robins; HPS (Heart Protection Study) R Collins, J Armitage, A Keech, S Parish, R Peto, P Sleight; IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid-lowering) T R Pedersen; JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) P M Ridker; LDS (Lipids in Diabetes Study) R Holman; LEADER (Lower Extremity Arterial Disease Event Reduction trial) T Meade; LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) J Simes, A Keech, S MacMahon, I Marschner, A Tonkin, J Shaw; LIPS (Lescol Intervention Prevention Study) P W Serruys; MEGA (Management of Elevated cholesterol in the primary prevention Group of Adult Japanese) H Nakamura; Post-CABG (Post- Coronary Artery Bypass Graft Study) G Knatterud; PPP (Pravastatin Pooling Project) C Furberg, R Byington; PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) P Macfarlane, S Cobbe, I Ford, M Murphy, G J Blauw, C Packard, J Shepherd; 4S Scandinavian Simvastatin Survival Study) J Kjekshus, T Pedersen, L Wilhelmsen; PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) E Braunwald, C Cannon, S Murphy; SEARCH (Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine) R Collins, J Armitage, L Bowman, S Parish, R Peto, P Sleight; SHARP (Study of Heart and Renal Protection) C Baigent, M Landray, R Collins; TNT (Treating to New Targets) J La Rosa; WHI (Women's Health Initiative) J Rossouw, J Probstfield; WOSCOPS (West of Scotland Coronary Prevention Study) J Shepherd, S Cobbe, P Macfarlane, I Ford. Other members: M Flather, J Kastelein, C Newman, C Shear, J Tobert, J Varigos, H White, S Yusuf.

CTT secretariat

E H Barnes, A C Keech, A Kirby, I C Marschner, J Simes (CTC, University of Sydney), C Baigent, L Blackwell, R Collins, J Emberson, W G Herrington, L E Holland, B Mihaylova, C Reith (CTSU, University of Oxford)

Conflicts of interest

The CTT Collaboration is funded by the UK Medical Research Council, British Heart Foundation, Cancer Research UK, and the Australian National Health and Medical Research

Council, and not by the pharmaceutical industry. Most of the trials in this report were supported (at least in part) by research grants from the pharmaceutical industry. Representatives of the pharmaceutical companies funding trials included in the CTT are invited to attend meetings and to comment on draft papers, but the final content of publications is determined by members of the writing committee. Some members of the writing committee have received reimbursement of costs to participate in scientific meetings from the pharmaceutical industry.

Acknowledgments

The National Health and Medical Research Council Clinical Trials Centre (CTC) in Australia and The Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) in the UK coordinate this collaboration jointly. The CTC is supported by a program grant from the Australian National Health and Medical Research Council and the CTSU by the UK Medical Research Council, British Heart Foundation and Cancer Research UK.

REFERENCES

1. 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.[erratum appears in Lancet. 2005 Oct 15-21;366(9494):1358]. Lancet. 2005; **366**(9493): 1267-78.
2. Cholesterol Treatment Trialists' (CTT) Collaborators. 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**(9753): 1670-81.
3. Ward S, Lloyd Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007; **11**(14): 1-160.
4. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012; **380**(9841): 581-90.
5. Walsh JM, Pignone M, Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. JAMA. 2004; **291**(18): 2243-52.
6. Abramson J, Wright JM. Are lipid-lowering guidelines evidence-based? Lancet. 2007; **369**(9557): 168-9.
7. Reidenberg MM. Statins for primary prevention of coronary artery disease. Lancet. 2007; **369**(9567): 1078; author reply 9.
8. Mascitelli L, Pezzetta F. Statins for primary prevention of coronary artery disease. Lancet. 2007; **369**(9567): 1078-9; author reply 9.
9. Taylor F, Ward K, Moore Theresa HM, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2011.
10. Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. Int J Cardiol. 2010; **138**(1): 25-31.
11. Reiner Z. Statins in the primary prevention of cardiovascular disease. Nat Rev Cardiol. 2013; **10**(8): 453-64.
12. Dale KM, Coleman CI, Shah SA, et al. Impact of gender on statin efficacy. Curr Med Res Opin. 2007; **23**(3): 565-74.
13. Hague W, Forder P, Simes J, et al. Effect of pravastatin on cardiovascular events and mortality in 1516 women with coronary heart disease: results from the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study. Am Heart J. 2003; **145**(4): 643-51.
14. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997; **96**(12): 4211-8.
15. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-Analysis of Statin Effects in Women Versus Men. JACC. 2012; **59**(6): 572-82.
16. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. Mayo Clin Proc. 2007; **82**(2): 166-70.
17. National Research Council. Women's Health Research: Progress, Pitfalls, and Promise. Washington, DC: The National Academies Press; 2010.
18. Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. Am J Cardiol. 1995; **75**(16): 1130-4.

19. Hocking RR. Analysis of Linear Models. Monterey, CA: Brooks-Cole; 1984.
20. 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**(11): 1307-16.
21. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [erratum appears in N Engl J Med. 2006 Feb 16;354(7):778]. N Engl J Med. 2004; **350**(15): 1495-504.
22. 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.[Erratum appears in JAMA. 2005 Dec 28;294(24):3092]. JAMA. 2005; **294**(19): 2437-45.
23. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in Older Patients with Systolic Heart Failure. N Engl J Med. 2007; **357**(22): 2248.
24. 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**(12): 810-20.
25. 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**(21): 2195-207.
26. Search Study Collaborative Group, Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. Am Heart J. 2007; **154**(5): 815-23.
27. Abraha I, Bonacini I, Montedori A, Abraha I, Bonacini I, Montedori A. Efficacy and safety of cholesterol-lowering treatment. Lancet. 2006; **367**(9509): 469; author reply 70-1.
28. Fenton A, Panay N. Statins in women for primary prevention--is there evidence to back up their use?? Climacteric. 2010; **13**(5): 403-4.
29. Eisenberg T, Wells MT. Statins and Adverse Cardiovascular Events in Moderate Risk Females: A Statistical and Legal Analysis with Implications for FDA Preemption Claims. SSRN; 2008.
30. Kim ESH, Menon V. Status of Women in Cardiovascular Clinical Trials. Arterioscler Thromb Vasc Biol. 2009; **29**(3): 279-83.
31. Taylor F, Huffman Mark D, Macedo Ana F, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev: John Wiley & Sons, Ltd; 2013.
32. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011; **32**(14): 1769-818.
33. Ajjan RA. Primary and secondary prevention of cardiovascular disease in diabetes with aspirin. Diab Vasc Dis Res. 2012; **9**(4): 243-4.
34. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline: National Institute for Health and Care Excellence; 2014. Report No.: 181.
35. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013.
36. Armitage J. The safety of statins in clinical practice. Lancet. 2007; **370**(9601): 1781-90.

37. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; **375**(9716): 735-42.
38. Preiss D, Seshasai SRK, Welsh P, et al. Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy. JAMA: The Journal of the American Medical Association. 2011; **305**(24): 2556-64.

Table and Figure legend

Table 1. Design features of 27 trials, with numbers of women and of those with a documented history of vascular disease.

Table 2. Demographic, clinical and biochemical characteristics in 27 trials.

In three of the more vs. less trials statin therapy was stopped before randomisation, requiring estimation of their baseline values by multiplying the values at the randomisation visit (ie, off statin treatment) by the mean proportional reduction observed at 1 year among those allocated the less intensive regimen.[20-22]

Figure 1. Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol, subdivided by history of vascular disease and gender

***** Adjusted heterogeneity test calculated from a Cox model that corrects for non-gender differences between women and men (see Methods and webappendix pp10-12)

+ Results for men with no known history of vascular disease included 189 vs 264 first MVEs from participants recruited into WOSCOPS in which information on prior stroke was not available.

Figure 2. Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender

***** Adjusted heterogeneity test calculated from a Cox model that corrects for non-gender differences between women and men (see Methods and webappendix)

Figure 3. Effects on components of major vascular events per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender

***** Adjusted heterogeneity test calculated from a Cox model that corrects for non-gender differences between women and men (see Methods and webappendix)

Figure 4. Effects on cause-specific mortality per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender

***** Adjusted heterogeneity test calculated from a Cox model that corrects for non-gender differences between women and men (see Methods and webappendix)

Table 1. Design features of 27 trials, with numbers of women and of those with a documented history of vascular disease

Trial	Median duration follow up (survivor years)*	Treatment comparison (mg/day)	Number of patients	Women		History of vascular disease‡	
				n	%	n	%
Statin vs. Control							
4S	5·4	S20–40 vs placebo	4444	827	19%	4444	100%
WOSCOPS	4·8	P40 vs placebo	6595	0	0%	499	8%
CARE	5.0	P40 vs placebo	4159	576	14%	4159	100%
Post-CABG	4·3	L40–80 vs L2·5–5	1351	102	8%	1351	100%
AFCAPS/ TexCAPS	5·2	L20–40 vs placebo	6605	997	15%	19	<1%
LIPID	6.0	P40 vs placebo	9014	1516	17%	9014	100%
GISSI Prevention	2.0	P20 vs no treatment	4271	587	14%	4271	100%
LIPS	3·9	F80 vs placebo	1677	271	16%	1677	100%
HPS	5·4	S40 vs placebo	20536	5082	25%	17375	85%
PROSPER	3·3	P40 vs placebo	5804	3000	52%	2550	44%
ALLHAT–LLT	4·9	P40 vs usual care	10355	5051	49%	2318	22%
ASCOT–LLA	3·3	A10 vs placebo	10305	1942	19%	1445	14%
ALERT	5·5	F40 vs placebo	2102	715	34%	400	19%
CARDS	4.1	A10 vs placebo	2838	909	32%	100	4%
ALLIANCE	4.7	A10-80 vs usual care	2442	434	18%	2442	100%
4D	4.0	A20 vs placebo	1255	578	46%	911	73%
ASPEN	4.0	A10 vs placebo	2410	811	34%	747	31%
MEGA‡‡	5.0	P10-20 vs usual care	8214	5547	68%	95	1%
JUPITER	2.0	R20 vs placebo	17802	6801	38%	0	0%
GISSI-HF	4.2	R10 vs placebo	4574	1032	23%	4574	100%
AURORA	4.6	R10 vs placebo	2773	1050	38%	1110	40%
CORONA	3.0	R10 vs placebo	5011	1180	24%	5011	100%
SUBTOTAL: 22 trials	**4.8†**		**134537**	**39008**	**29%**	**64512**	**48%**

More vs. Less statin							
PROVE-IT	2.1	A80 vs P40	4162	911	22%	4162	100%
A to Z	2.0	S40 then S80 vs. Placebo then S20	4497	1100	24%	4497	100%
TNT	5.0	A80 vs. A10	10001	1902	19%	10001	100%
IDEAL	4.8	A40-80 vs. S20-40	8888	1702	19%	8888	100%
SEARCH	7.0	S80 vs. S20	12064	2052	17%	12064	100%
SUBTOTAL: (5 trials)	**5.1†**		**39612**	**7667**	**19%**	**39612**	**100%**
TOTAL: 27 trials	**4.9†**		**174149**	**46675**	**27%**	**104124**	**60%**

* Estimated using Kaplan-Meier method with patients censored at their date of death

† weighted by trial-specific variances of observed logrank (o–e) for major vascular events

‡ History of CHD, intracerebral bleed, transient ischaemic attack, stroke, peripheral artery disease or heart failure.

‡‡ Includes 382 randomised patients who were excluded from the original publication.

PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy. A=atorvastatin. P=pravastatin. A to Z=Aggrastat to Zocor. S=simvastatin. TNT=Treating to New Targets. IDEAL=Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group. SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SSSS=Scandinavian Simvastatin Survival Study.WOSCOPS=West of Scotland Coronary Prevention Study. CARE=Cholesterol And Recurrent Events. Post-CABG=Post-Coronary Artery Bypass Graft. L=lovastatin. AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. LIPID=Long–term Intervention with Pravastatin in Ischaemic Disease. GISSI–P=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. LIPS=Lescol Intervention Prevention Study. F=fluvastatin. HPS=Heart Protection Study. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm. ALERT=Assessment of Lescol in Renal Transplantation. CARDS=Collaborative Atorvastatin Diabetes Study. ALLIANCE=Aggressive Lipid-Lowering Initiation Abates New Cardiac Events. 4D=Die Deutsche Diabetes Dialyse Studie. ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus. MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group. JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group. R=rosuvastatin. GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiac. AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events.

Table 2. Demographic, clinical and biochemical characteristics in 27 trials

	Statin vs control (22 trials)		More vs less (5 trials)		Statin/more vs control/less (27 trials)	
	Women (n=39,008)	Men (n=95,485)	Women (n=7,667)	Men (n=31,944)	Women (46,675)	Men (127,429)
Age (years) [mean(SD)]	65.3 (8.9)	62.0 (9.4)	63.8 (9.6)	61.1 (9.6)	65.1 (9.1)	61.8 (9.5)
Current Smoker	6019 (15.4%)	19614 (20.5%)	1594 (20.8%)	6435 (20.1%)	7613 (16.3%)	26049 (20.4%)
BMI (kg/m^2) [med(IQR)]	27.1 (23.8 - 31.1)	26.8 (24.5 - 29.6)	27.8 (24.6 - 31.6)	27.5 (25.2 - 30.1)	27.2 (23.9 - 31.2)	27.0 (24.7 - 29.7)
Hypertension	23678 (60.7%)	47087 (49.3%)	4306 (56.2%)	13432 (42.0%)	27984 (60.0%)	60519 (47.5%)
Systolic BP (mmHg) [mean(SD)]	141.2 (21.1)	139.3 (21.4)	135.5 (21.2)	133.1 (19.5)	140.4 (21.2)	137.8 (21.1)
Diastolic BP (mmHg) [mean(SD)]	80.7 (11.1)	82.0 (11.5)	76.6 (11.2)	78.7 (10.8)	80.1 (11.2)	81.3 (11.4)
History of vascular disease	14102 (36.2%)	50409 (52.8%)	7667 (100%)	31944 (100%)	21769 (46.6%)	82353 (64.6%)
Previous MI	5961 (15.3%)	29585 (40.0%)	5069 (66.1%)	23249 (72.8%)	11030 (23.6%)	52834 (41.5%)
Other symptomatic CHD	8538 (21.9%)	30844 (32.3%)	5230 (68.2%)	21603 (67.6%)	13768 (29.5%)	52447 (41.2%)
History of diabetes mellitus	9576 (24.5%)	18481 (19.4%)	1429 (18.6%)	4201 (13.2%)	11005 (23.6%)	22682 (17.8%)
Total Cholesterol (mmol/L) [mean(SD)]	5.8 (1.0)	5.6 (1.0)	4.6 (0.8)	4.3 (0.8)	5.6 (1.0)	5.3 (1.1)
LDL Cholesterol (mmol/L) [mean(SD)]	3.6 (0.9)	3.6 (0.9)	2.5 (0.7)	2.5 (0.6)	3.4 (0.9)	3.3 (1.0)
HDL Cholesterol (mmol/L) [mean(SD)]	1.4 (0.4)	1.1 (0.3)	1.3 (0.4)	1.1 (0.3)	1.3 (0.4)	1.1 (0.3)
Triglycerides (mmol/L) [med(IQR)]	1.5 (1.1 - 2.1)	1.6 (1.2 - 2.2)	1.6 (1.2 - 2.2)	1.6 (1.2 - 2.2)	1.5 (1.1 - 2.1)	1.6 (1.2 - 2.2)
Creatinine (μmol/L) [med(IQR)]	79.6 (70.7 - 91.0)	97.2 (88.4 - 110.0)	82.9 (72.3 - 97.2)	97.2 (88.4 - 108.9)	79.6 (70.7 - 92.0)	97.2 (88.4 - 110.0)

Abbreviations: MI = Myocardial Infarction; CHD = Coronary heart disease; BP = Blood Pressure; BMI = Body Mass Index; LDL = Low density lipoprotein; HDL = High density lipoprotein.

Characteristics displayed as averaged values of both randomised trial arms

P=NS within each sex for all comparisons of baseline characteristics between randomised armstrial type (statin vs. control and more vs. less)

P<0.0001 for all comparisons between men and women in the combined statin/control and more/less population

Figure 1: Effects on MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by history of vascular disease and gender

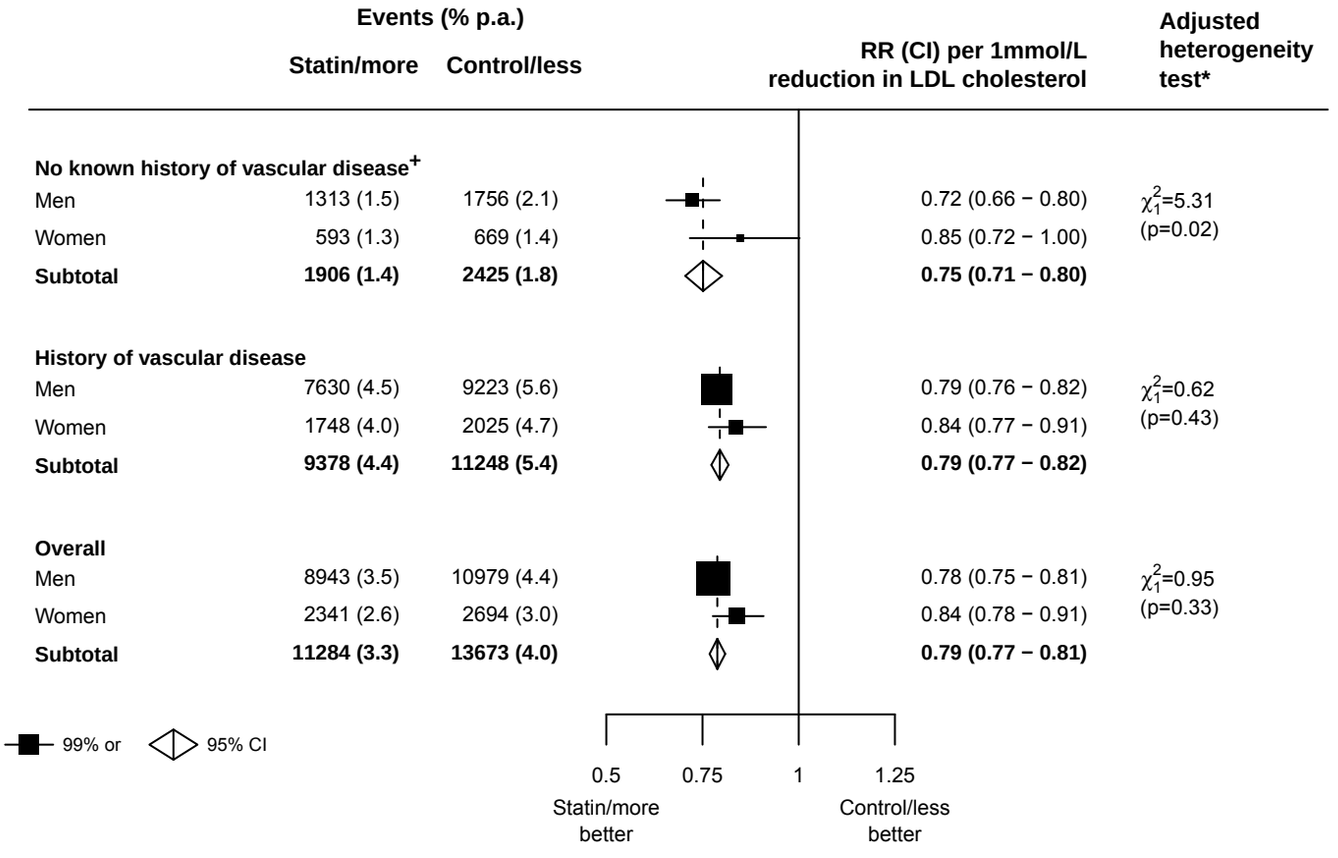


Figure 2: Effects on MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender

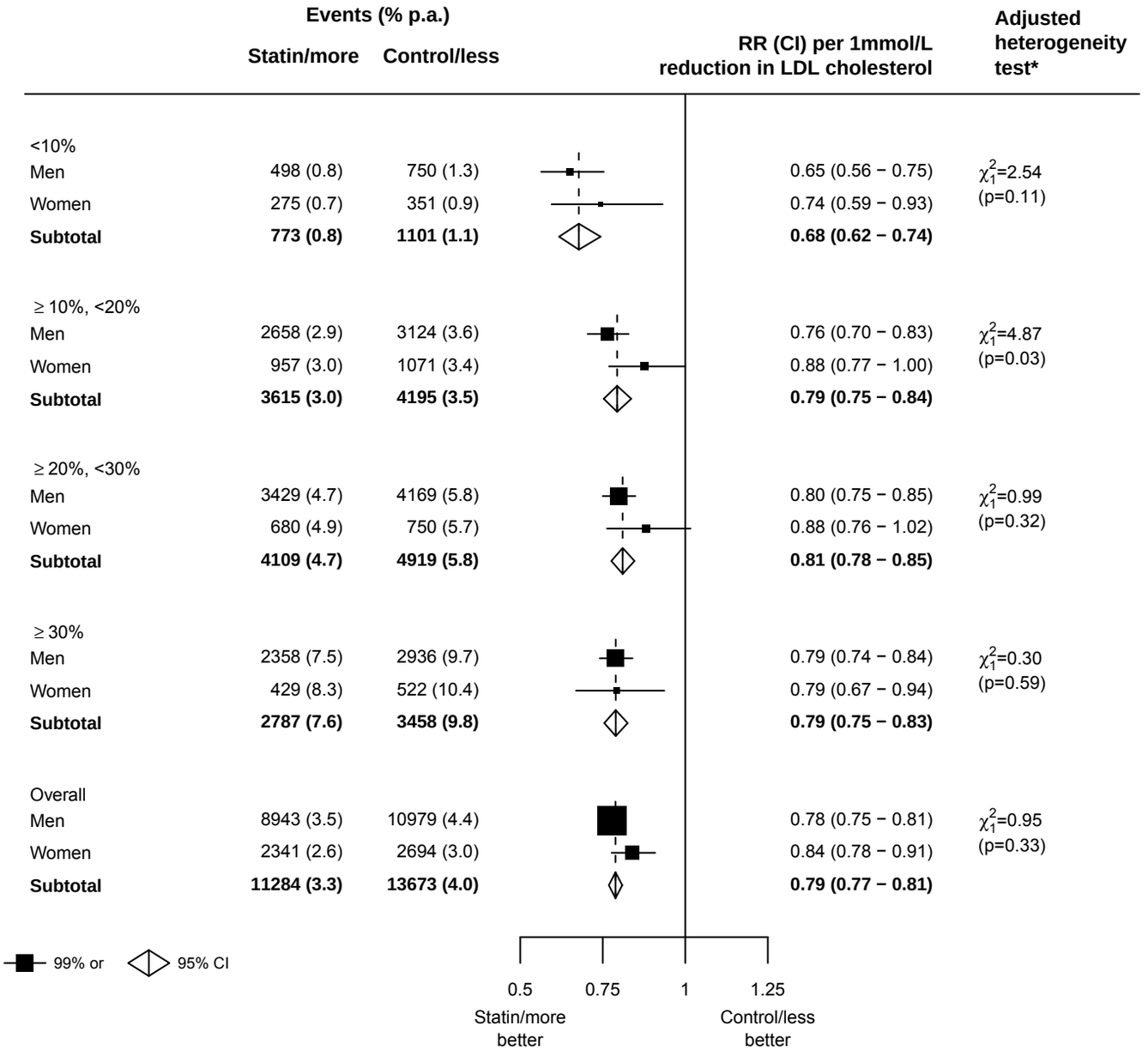


Figure 3: Effects on components of MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender

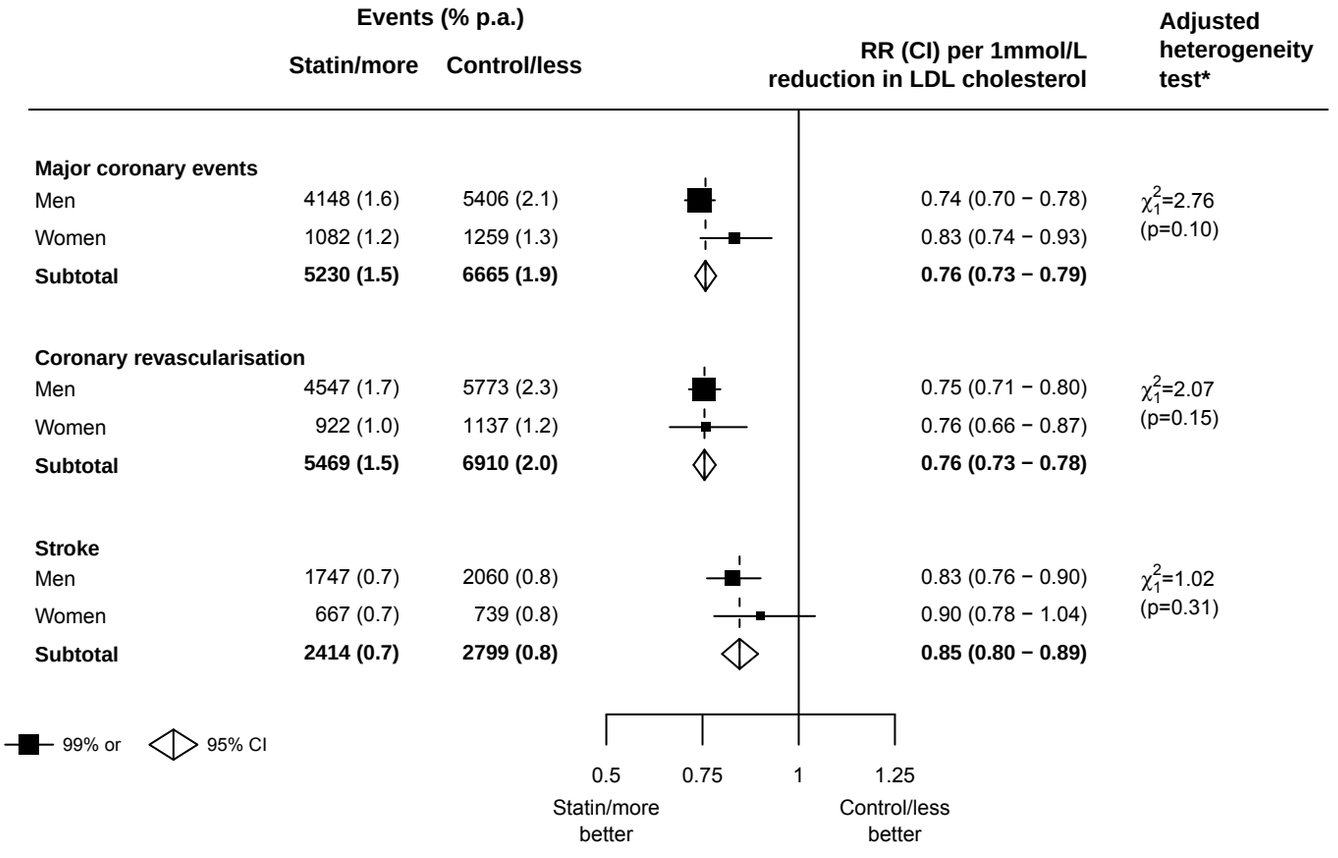
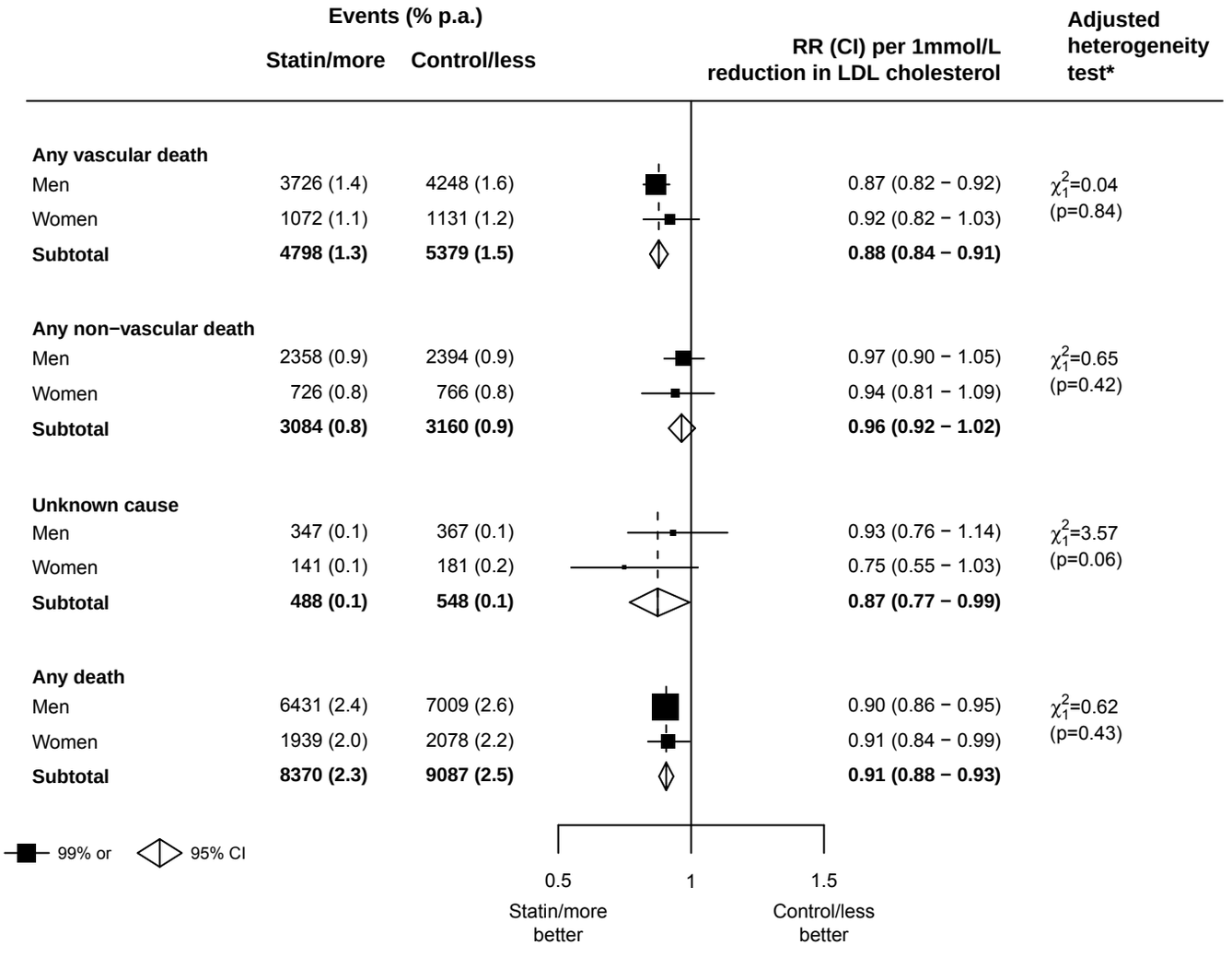


Figure 4: Effects on CAUSE−SPECIFIC MORTALITY per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender



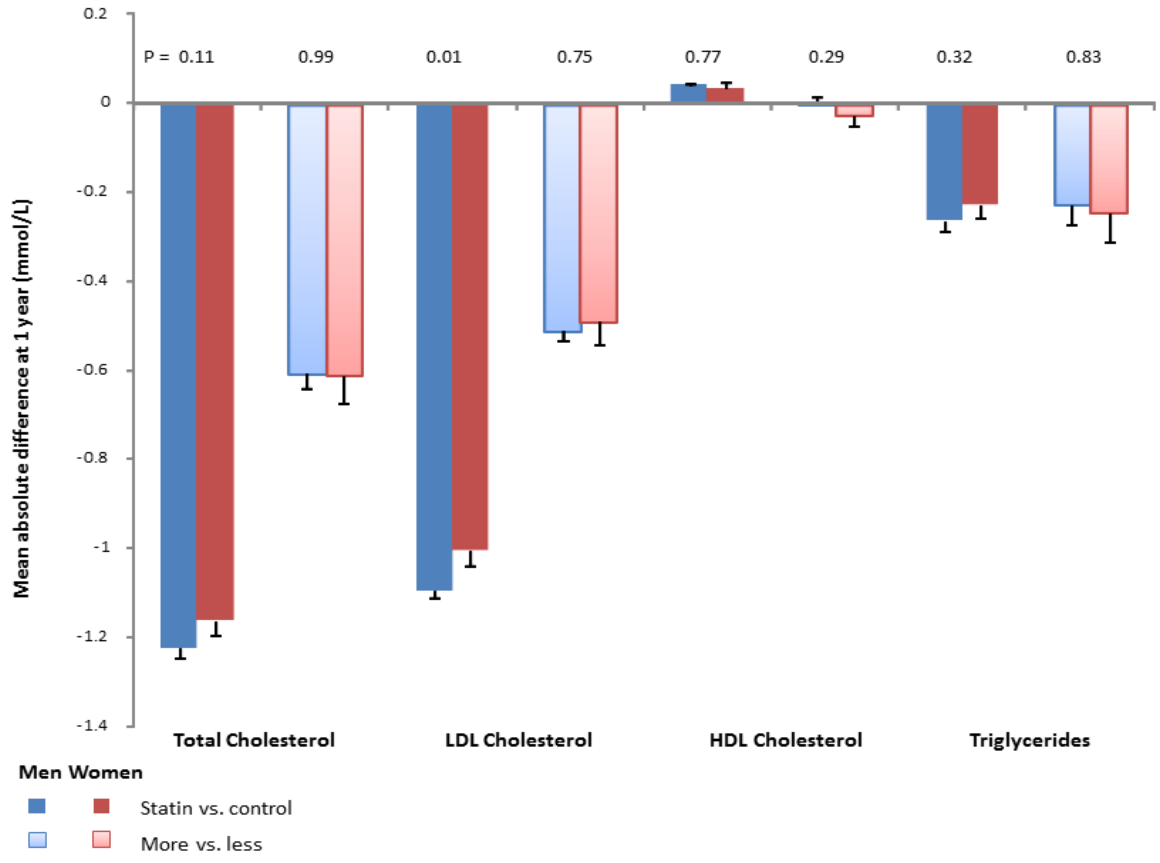
Online webappendix

Efficacy and safety of LDL-lowering therapy among women and men: meta-analysis of individual data from 174,000 participants in 27 randomised trials

Webfigures

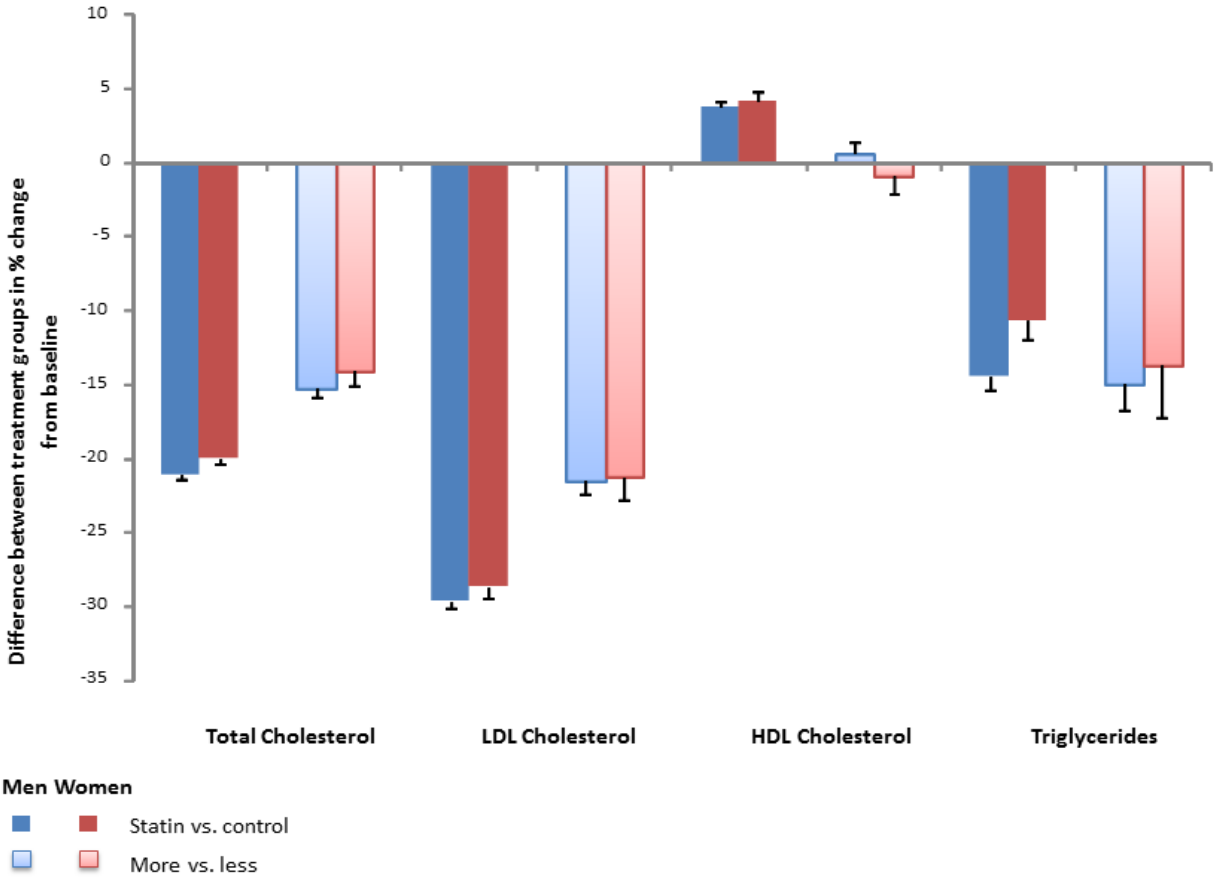
Webfigure 1: Absolute (panel A) and proportional (panel B) differences in treatment group mean lipid levels at 1 year by gender in statin vs control and more vs less trials

A



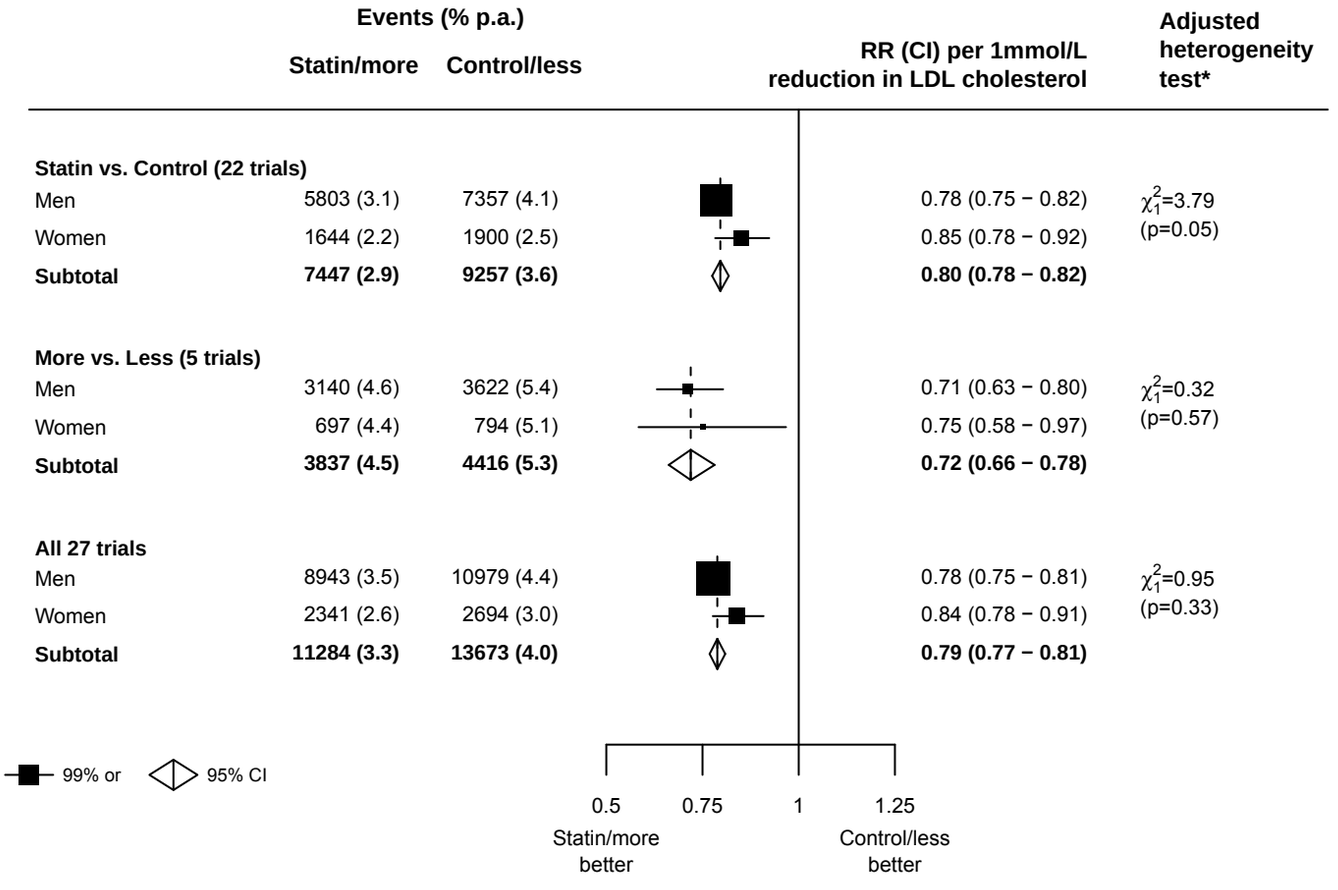
Heterogeneity p values by sex and standard error bars displayed

B



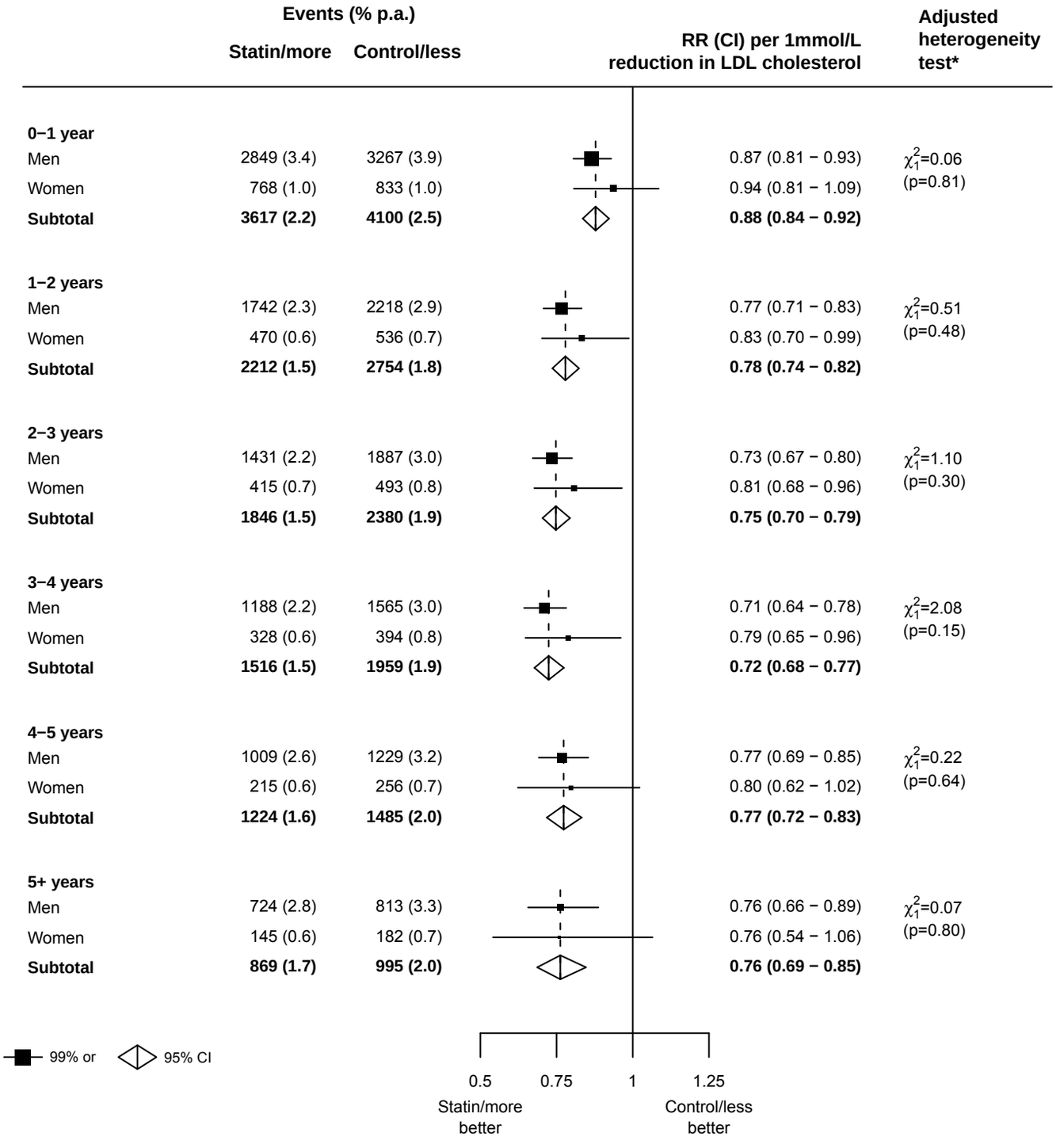
Standard error bars displayed

Webfigure 2: Effects on MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by type of trial and gender



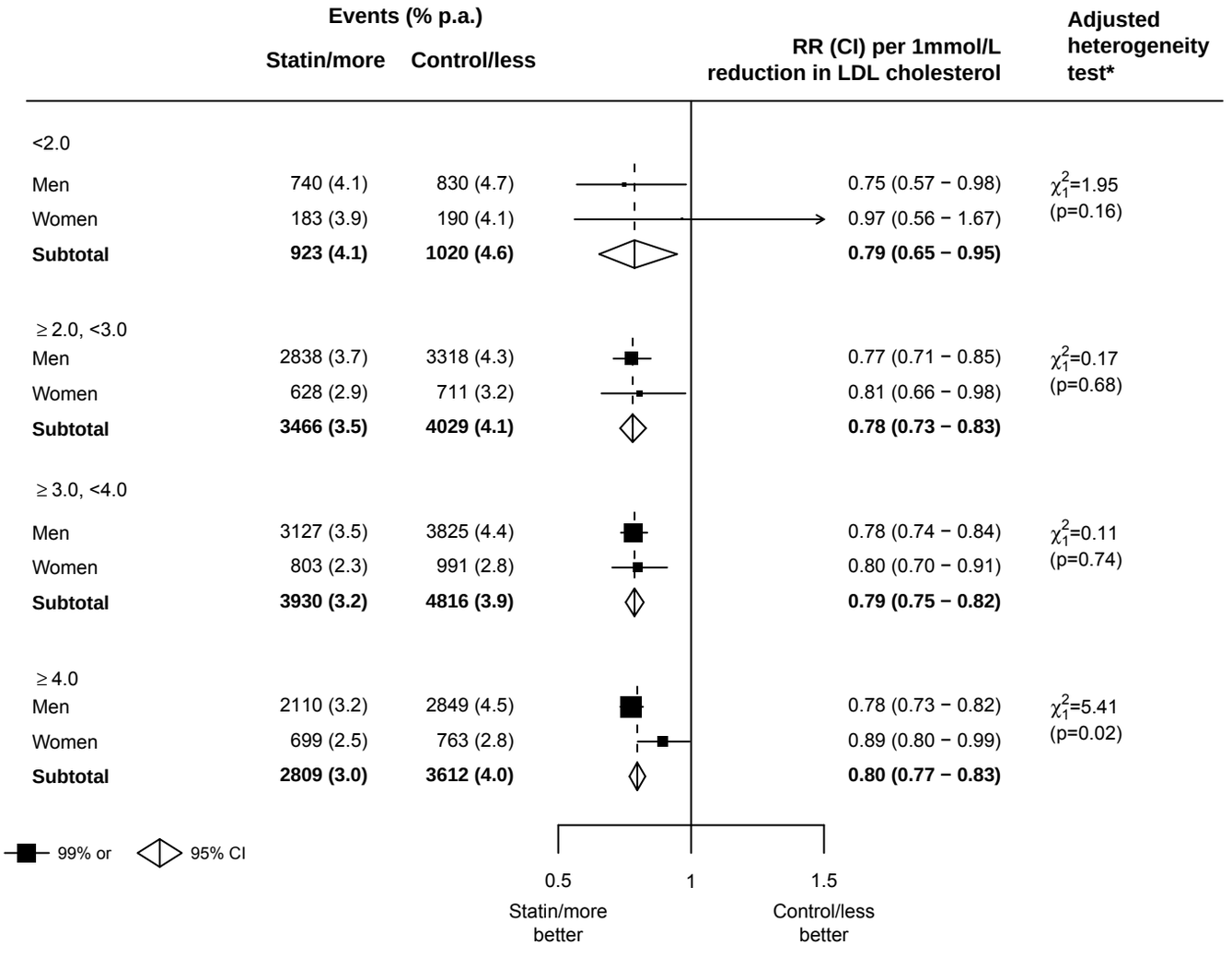
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 3: Effects on MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by duration of treatment and gender



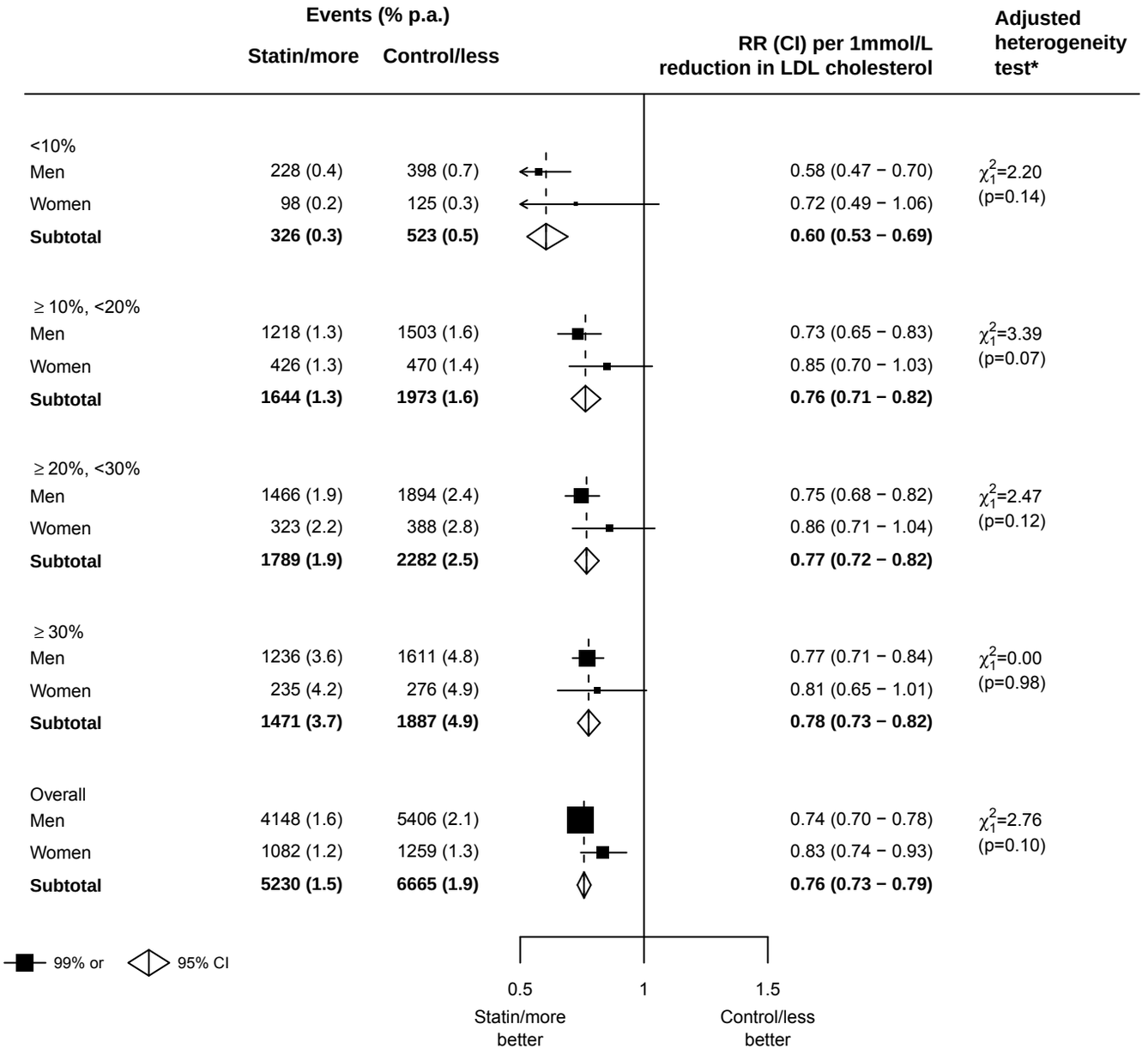
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 4: Effects on MAJOR VASCULAR EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by baseline LDL cholesterol and gender



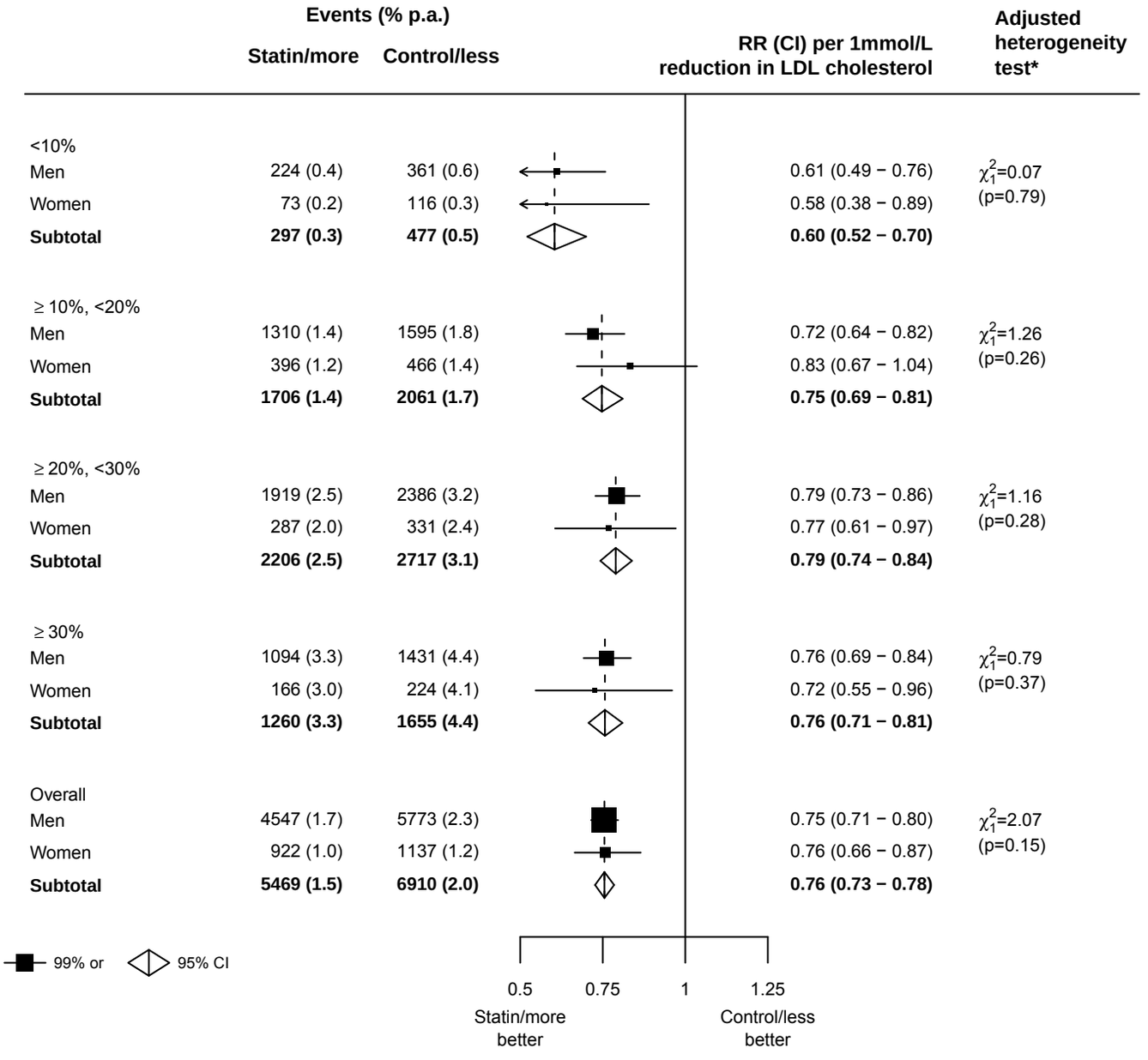
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 5: Effects on MAJOR CORONARY EVENTS per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender



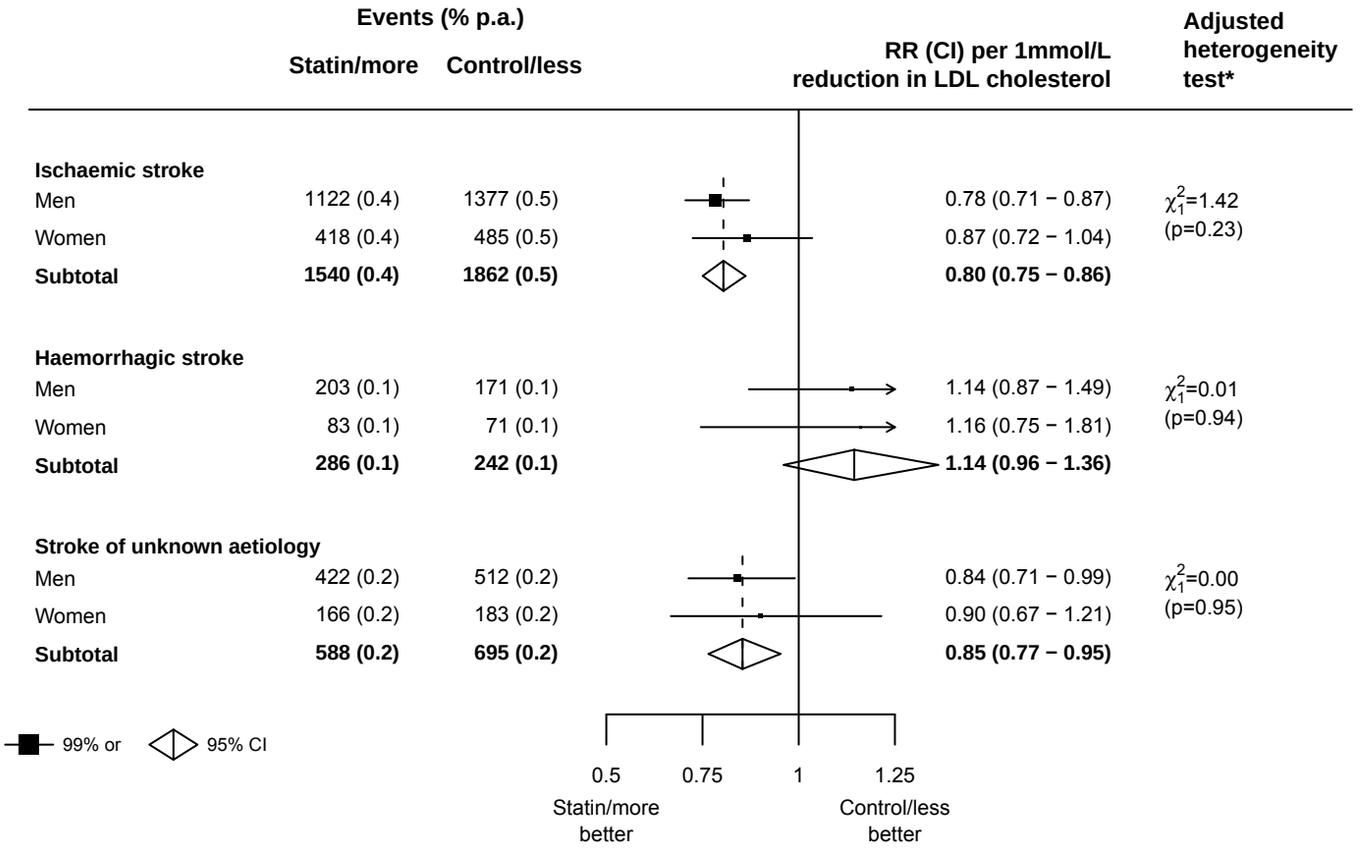
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 6: Effects on CORONARY REVASCULARISATION per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender



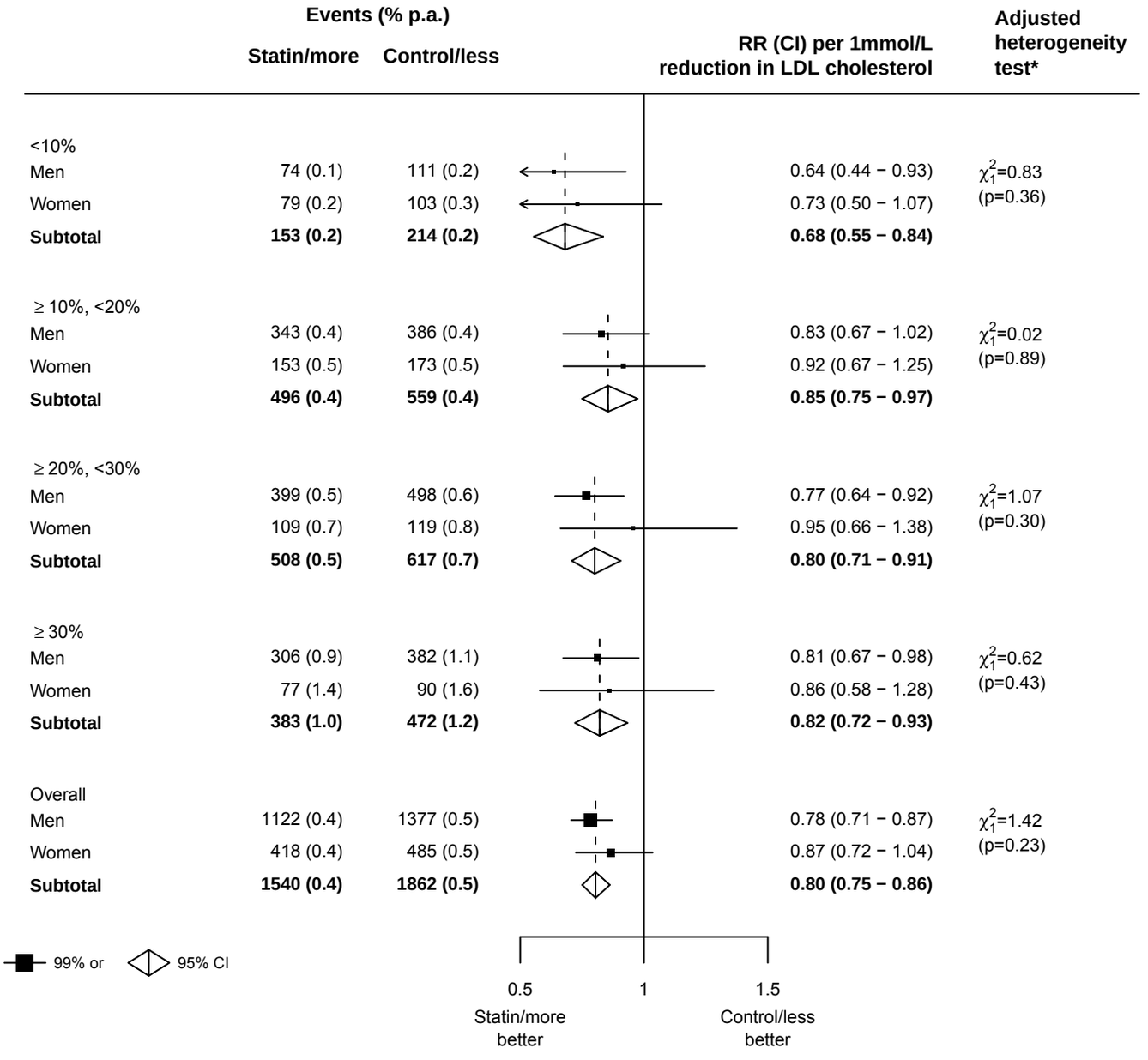
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 7: Effects on STROKE SUBTYPES per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender



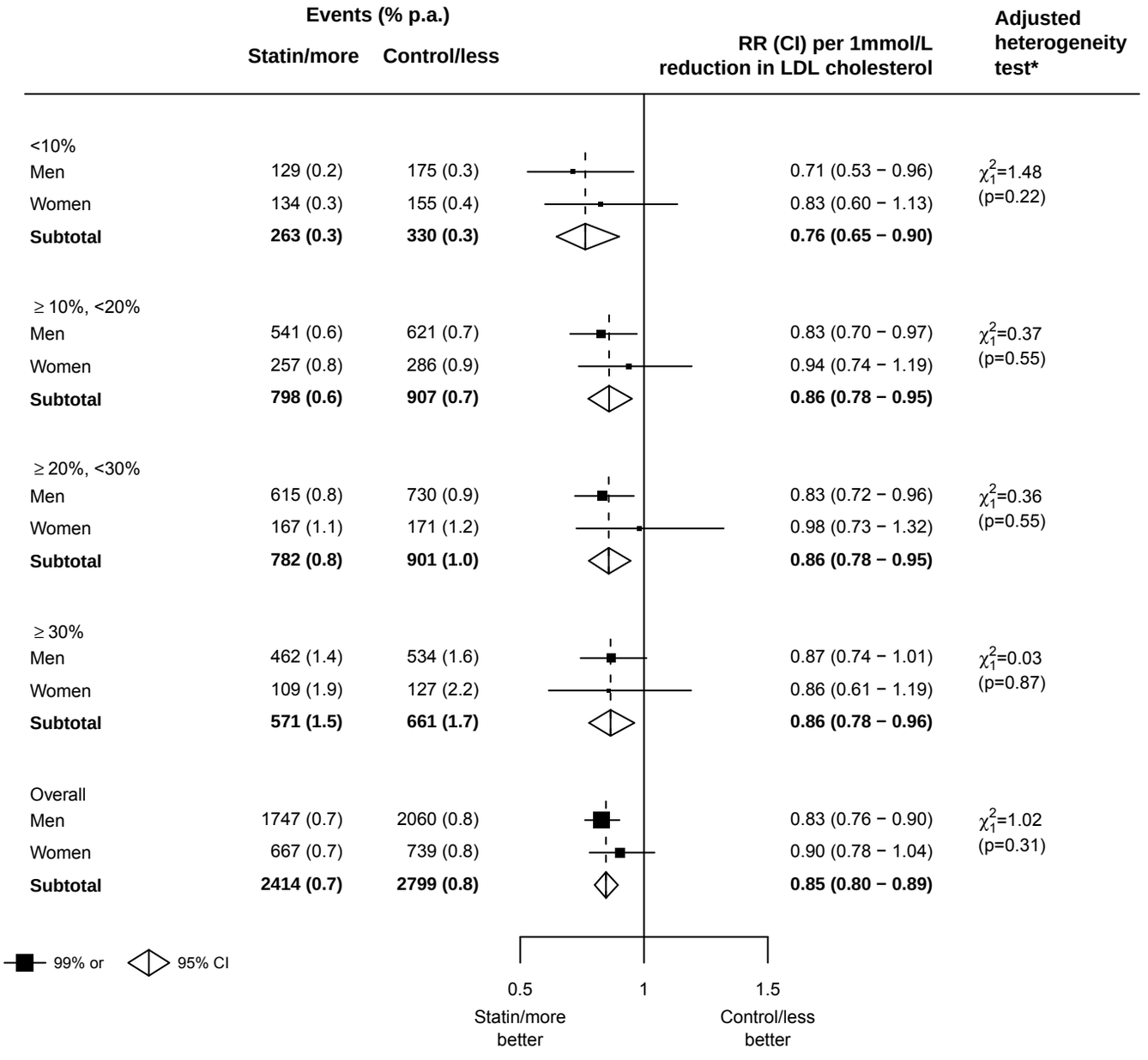
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 8: Effects on ISCHAEMIC STROKE per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender



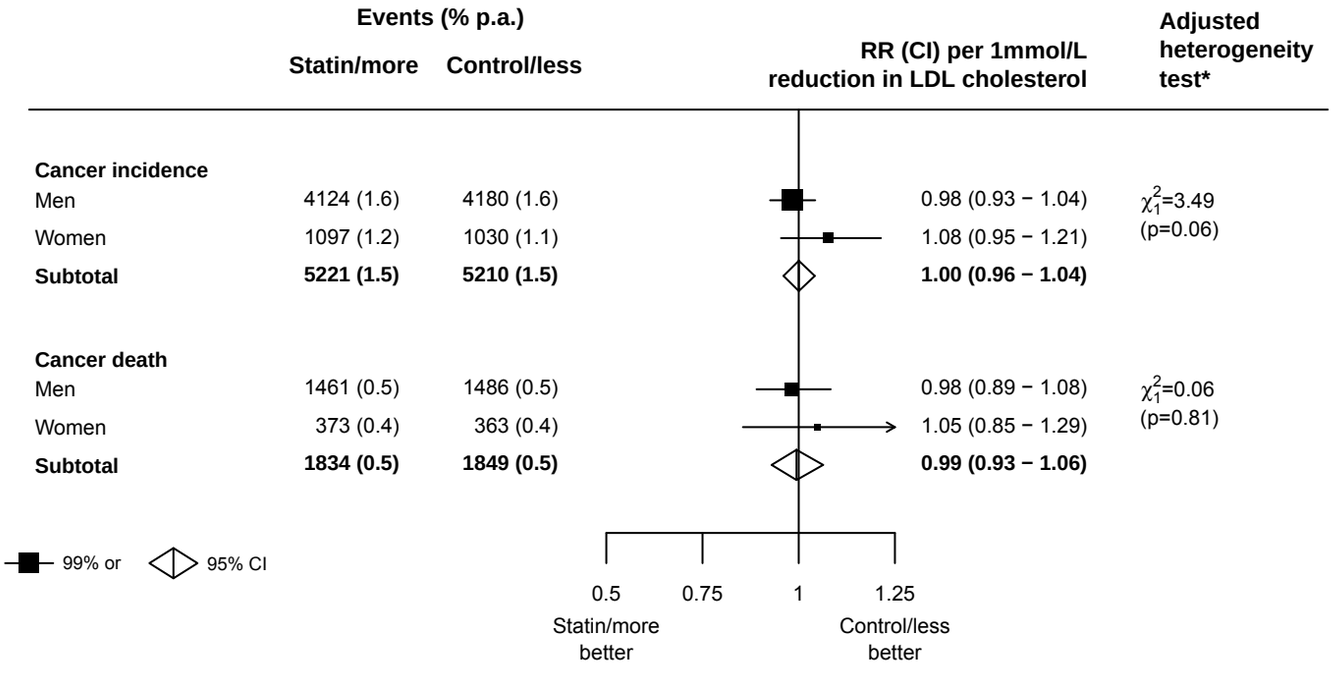
* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 9: Effects on ANY STROKE per 1.0 mmol/L reduction in LDL cholesterol, subdivided by 5−year vascular risk at baseline and gender



* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Webfigure 10: Effects on CANCER INCIDENCE and CANCER DEATH per 1.0 mmol/L reduction in LDL cholesterol, subdivided by gender



* Adjusted heterogeneity test calculated from a Cox model that corrects for non−gender differences between women and men (see Methods and webappendix, p 14)

Statistical appendix

Estimating the five year risk of major vascular event among the participants in 27 randomised trials of statin therapy

The 5-year risk of a major vascular event (first non-fatal myocardial infarction, coronary death, stroke or coronary revascularisation procedure) was estimated using separate Cox proportional hazards models for the 67,000 patients allocated the control regimen in the 22 trials of statin versus control (model 1) and the 20,000 patients allocated the less intensive statin regimen in the 5 trials of more versus less statin (model 2). The results from these two regression models were then applied to all patients (including those in the active treatment arms), as described below.

For patient *i* in study *j* with allocated treatment *k* (where *k*=0 corresponds to the control/less statin treatment and *k*=1 corresponds to the statin/more statin treatment), the hazard function in the control/less statin group was modelled by the regression equation:

$$h_{ij0}(t) = h_0(t)exp(\alpha + \beta_j + \gamma(x_{ij0} - \bar{x}_{.j0}) + \delta(w_{ij0}) + \theta(z_j(t)))$$

where $h_0(t)$ is the baseline hazard function, α is an overall intercept term, β_j represents the effect of study j relative to the Heart Protection Study for model 1 or the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine for model 2 (see Statistical appendix table, terms C), γ represents a vector of log hazard ratios corresponding to the patient's set of baseline characteristics x_{ij0} (centred around study means $\bar{x}_{.j0}$ where appropriate: see Statistical appendix table, terms A), δ represents a vector of log hazard ratios corresponding to interactions w_{ij0} between various baseline characteristics (see Statistical appendix table, terms B), and θ represents a vector of log hazard ratios corresponding to trial-specific time dependent effects $z_j(t)$ (defined for initial six-monthly time periods: see Statistical appendix table, terms D).

For each of the two regression models, the baseline characteristics x_{ij} and interactions w_{ij} were selected using backward elimination, with factors remaining in the model if they were statistically significant at the 1% level (age and sex were to be included in both models irrespective of statistical significance). The baseline characteristics included in the final models are shown in the Statistical appendix table. The trial-specific time dependent effects $z_j(t)$ were defined for initial six-monthly time periods and a backwards elimination strategy with statistical significance at 1% was employed to select the effects remaining in the models.

The Cox models provide estimates of log hazard ratios, but provide no direct estimate of the baseline hazard$h_o(t)$. However, an estimate of the cumulative hazard function $H_o(t)$ can be recovered by estimation of baseline hazard contributions at failure times using the Kalbfleisch and Prentice method and, from that, an estimate of the baseline cumulative survival $S_0(t) = \exp(-H_0(t))$ can be made.

Separating study participants according to baseline 5-year major vascular event risk

The predicted 5-year risk of a major vascular event for all patients was estimated by:

$$P_{ijk}(t) = 1 - S_0(t)^{exp(\alpha+\beta_j+\gamma(x_{ijk}-\bar{x}_{.j0})+\delta(w_{ijk})+\theta(z_j(t)))} \quad \text{at t=5 years}$$

Trial participants were categorised into baseline categories of 5-year risk: <5%; 5 to <10%; 10 to <20%; 20 to <30%; and 30% or larger.

Statistical appendix table: Cox proportional hazard models predicting the risk of a first major vascular event in participants allocated to control (model 1) or less statin (model 2)

Parameter	Model 1 Statin vs. Control	Model 2 More vs. less statin
	Hazard ratio (95% CI)	**Hazard ratio (95% CI)**
A. Baseline characteristics		
Male gender	1.56 (1.45 - 1.69)	1.07 (0.98 - 1.16)
Current smoker	1.43 (1.28 - 1.60)	1.27 (1.18 - 1.38)
Age (per 10 years) §	1.41 (1.35 - 1.48)	1.12 (1.08 - 1.16)
Natural logarithm of HDL (per 1 lnmmol/L) §	0.69 (0.63 - 0.75)	0.76 (0.68 - 0.86)
LDL (per 1 mmol/L) §	1.14 (1.11 - 1.18)	1.19 (1.13 - 1.25)
Treatment for hypertension	1.23 (1.17 - 1.29)	1.15 (1.08 - 1.22)
Systolic BP (per 20mmHg) §	1.18 (1.13 - 1.23)	
Diastolic BP (per 10mmHg) §	0.95 (0.93 - 0.97)	
Creatinine (per 50µmol/L) §*	1.18 (1.12 - 1.23)	1.19 (1.10 - 1.28)
History of MI	2.50 (2.23 - 2.81)	1.19 (1.07 - 1.32)
History of other CHD, but no MI	1.83 (1.69 - 1.97)	
History of stroke	1.35 (1.25 - 1.46)	1.48 (1.33 - 1.64)
History of PAD	1.24 (1.16 - 1.32)	1.38 (1.24 - 1.54)
Other/nonspecific vascular disease history†	1.22 (1.06 - 1.42)	
History of diabetes mellitus	1.53 (1.45 - 1.62)	1.40 (1.29 - 1.51)
B. Interaction terms #		
Age and history of MI (per 10 years)	0.74 (0.70 - 0.79)	
Age and history of other CHD (per 10 years)	0.77 (0.71 - 0.83)	
Systolic BP and history of MI	0.91 (0.86 - 0.95)	
Systolic BP and other CHD	0.89 (0.84 - 0.94)	
Current smoker and male gender	0.80 (0.71 - 0.9)	
Male gender and history of MI	0.78 (0.70 - 0.87)	
C. Trial-specific terms (to model average risk)		
SSSS	1.95 (1.78 - 2.13)	
WOSCOPS	0.91 (0.79 - 1.04)	
CARE	1.25 (1.13 - 1.39)	
Post-CABG	0.88 (0.72 - 1.07)	
AFCAPS/TexCAPS	0.55 (0.47 - 0.65)	
LIPID	1.06 (0.98 - 1.15)	
GISSI-P	0.74 (0.59 - 0.92)	
ASCOT-LLA	0.65 (0.56 - 0.75)	
PROSPER	2.00 (1.80 - 2.22)	
CARDS	0.67 (0.55 - 0.81)	
ALERT	0.87 (0.73 - 1.04)	

ALLHAT-LLT	1.19 (1.07 - 1.32)	
LIPS	1.11 (0.87 - 1.42)	
ALLIANCE	1.51 (1.33 - 1.73)	
ASPEN	0.81 (0.67 - 0.97)	
4D	1.93 (1.63 - 2.28)	
MEGA	0.32 (0.26 - 0.39)	
JUPITER	0.48 (0.41 - 0.57)	
GISSI-HF	0.47 (0.37 - 0.60)	
AURORA	2.78 (2.46 - 3.14)	
CORONA	0.95 (0.79 - 1.16)	
A to Z		0.59 (0.40 - 0.86)
PROVE-IT		1.76 (1.39 - 2.23)
TNT		1.37 (1.24 - 1.51)
IDEAL		1.21 (1.09 - 1.35)
D. Trial and period-specific terms		
GISSI-P; months 0 to 6	4.27 (3.21 - 5.67)	
LIPS; months 0 to 6	4.00 (2.82 - 5.66)	
LIPS; months 7 to 12	2.96 (1.99 - 4.40)	
GISSI-HF; months 0 to 6	1.75 (1.20 - 2.56)	
A to Z; months 0 to 6		7.77 (5.03 - 12.02)
A to Z; months 7 to 12		2.44 (1.51 - 3.95)
PROVE-IT; months 0 to 6		3.78 (2.77 - 5.16)
PROVE-IT; months 7 to 12		2.02 (1.46 - 2.79)
TNT; months 0 to 6		1.41 (1.11 - 1.80)
IDEAL; months 0 to 6		3.12 (2.48 - 3.93)
IDEAL; months 7 to 12		1.39 (1.10 - 1.75)

HDL= high-density lipoprotein cholesterol. LDL= low-density lipoprotein cholesterol. BP=blood pressure.
MI=myocardial infarction. CHD=coronary heart disease. PAD=peripheral arterial disease
* missing creatinine values at randomisation in ASCOT were replaced with creatinine measured at screening; in AFCAPS/TexCAPS, AURORA and 4D creatinine data were either not available (AFCAPS/TexCAPS) or not relevant (dialysis patients in AURORA/4D) and so centred values of 0 were used
§ centred around study mean
†defined as history of myocardial infarction or stroke for ALLHAT; history of heart failure in GISSI-HF and CORONA; carotid artery disease, carotid stenosis ≥50%, carotid endarterectomy and abdominal aortic aneurysm in AURORA
interpretation of the effects of the separate characteristics in these interactions should be based both on relevant main effects (part A) and the interaction effects (part B)

Statistical test for heterogeneity of treatment effects in women and men

A Cox proportional hazards regression model, stratified by trial, with age, diabetes, smoking, hypertension, history of vascular disease (defined as known coronary heart disease, cerebrovascular disease, or peripheral vascular disease), a treatment and male gender interacted with the weighted treatment allocation variable was used to test for heterogeneity of treatment effects in women and men.

For patient *i* in study *j* with allocated treatment *k* (where *k*=0 corresponds to the control/less statin treatment and *k*=1 corresponds to the statin/more statin treatment), the hazard function was modelled by the regression equation:

$$h_{ijk}(t) = h_{0j}(t)\exp\left(\alpha + \beta\left(x_{ijk}\right) + \delta\left(w_{ijk}\right)\right)$$

where $h_{0j}(t)$ is the baseline hazard function for study j , α is an overall intercept term, β_j represents a vector of log hazard ratios corresponding to the patient's set of baseline characteristics x_{ijk} that differ between women and men (i.e. age, diabetes, smoking, hypertension, history of vascular disease), male gender and allocation to treatment variable weighted by one-year LDL reduction in the respective trial, δ represents the log hazard ratio corresponding to the interaction w_{ijk} between male gender and the weighted allocation to treatment variable.