Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Summary

Background Results of previous randomised trials have shown that interventions that lower LDL cholesterol concentrations can significantly reduce the incidence of coronary heart disease (CHD) and other major vascular events in a wide range of individuals. But each separate trial has limited power to assess particular outcomes or particular categories of participant.

Methods A prospective meta-analysis of data from 90 056 individuals in 14 randomised trials of statins was done. Weighted estimates were obtained of effects on different clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings During a mean of 5 years, there were 8186 deaths, 14 348 individuals had major vascular events, and 5103 developed cancer. Mean LDL cholesterol differences at 1 year ranged from 0·35 mmol/L to 1·77 mmol/L (mean 1·09) in these trials. There was a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol (rate ratio [RR] 0·88, 95% CI 0·84–0·91; p<0·0001). This reflected a 19% reduction in coronary mortality (0·81, 0·76–0·85; p<0·0001), and non-significant reductions in non-coronary vascular mortality (0·93, 0·83–1·03; p=0·2) and non-vascular mortality (0·95, 0·90–1·01; p=0·1). There were corresponding reductions in myocardial infarction or coronary death (0·77, 0·74–0·80; p<0·0001), in the need for coronary revascularisation (0·76, 0·73–0·80; p<0·0001), in fatal or non-fatal stroke (0·83, 0·78–0·88; p<0·0001), and, combining these, of 21% in any such major vascular event (0·79, 0·77–0·81; p<0·0001). The proportional reduction in major vascular events differed significantly (p<0·0001) according to the absolute reduction in LDL cholesterol achieved, but not otherwise. These benefits were significant within the first year, but were greater in subsequent years. Taking all years together, the overall reduction of about one fifth per mmol/L LDL cholesterol reduction translated into 48 (95% CI 39–57) fewer participants having major vascular events per 1000 among those with pre-existing CHD at baseline, compared with 25 (19–31) per 1000 among participants with no such history. There was no evidence that statins increased the incidence of cancer overall (1·00, 0·95–1·06; p=0·9) or at any particular site.

Interpretation Statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol, largely irrespective of the initial lipid profile or other presenting characteristics. The absolute benefit relates chiefly to an individual's absolute risk of such events and to the absolute reduction in LDL cholesterol achieved. These findings reinforce the need to consider prolonged statin treatment with substantial LDL cholesterol reductions in all patients at high risk of any type of major vascular event.

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Introduction

Results of observational studies in different populations indicate a continuous positive relationship between coronary heart disease (CHD) risk and blood cholesterol concentrations that extends well below the range seen in many developed populations, without any definite threshold below which a lower cholesterol concentration is not associated with lower risk.[1,2] Despite this evidence, there has been substantial uncertainty about the effects on mortality and major morbidity of lowering blood cholesterol by drugs or diets.[3–9]

Definitive assessment of whether a substantial reduction in LDL cholesterol concentrations would be beneficial was facilitated by the development of potent cholesterol-lowering drugs, such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins).[10] But discussion among the principal investigators of ongoing large-scale randomised trials of these treatments suggested that some uncertainties about their effects were likely to persist unless there was a systematic meta-analysis of the findings; although the individual trials might be large enough to show effects on the aggregate of all coronary events, they might well over estimate or under estimate any effects on coronary death or on other specific vascular or non-vascular outcomes, especially when particular subgroups of participants were considered. Hence, in 1994, the decision was made to undertake periodic meta-analyses of individual participant data on mortality and morbidity from all relevant large-scale randomised trials of lipid-modifying treatments whose first results would be reported subsequently. This report is of the results from

	Dates of recruitment	Year of publication of primary results	Mean duration of follow-up (years)*	Treatment comparison (mg/day)†	Number of patients	Age range (years)	Women (%)	Diabetes (%)	Baseline history of vascular disease (%)			
									MI	Other CHD‡	Other vascular§	None¶
4S	5/1988–8/1989	1994	5·2	S20–40 *vs* placebo	4444	35–70	827 (19%)	202 (5%)	3530 (79%)	914 (21%)	126 (3%)	0
WOSCOPS	2/1989–9/1991	1995	4·8	P40 *vs* placebo	6595	45–64	0	76 (1%)	0	338 (5%)	193 (3%)	6096 (92%)
CARE	12/1989–12/1991	1996	4·8	P40 *vs* placebo	4159	21–75	576 (14%)	586 (14%)	4159 (100%)	0	0	0
Post-CABG	3/1989–8/1991	1997	4·2	L40–80 *vs* L2·5–5	1351	21–74	102 (8%)	116 (9%)	662 (49%)	689 (51%)	37 (3%)	0
AFCAPS/ TexCAPS	5/1990–2/1993	1998	5·3	L20–40 *vs* placebo	6605	45–73 (men) 55–73 (women)	997 (15%)	155 (2%)	0	10 (<1%)	9 (<1%)	6431 (97%)
LIPID	6/1990–12/1992	1998	5·6	P40 *vs* placebo	9014	31–75	1516 (17%)	782 (9%)	5754 (64%)	3248 (36%)	905 (10%)	10 (<1%)
GISSI Prevention	1/1994–5/1996	2000	1·9	P20 *vs* no treatment	4271	19–90	587 (14%)	582 (14%)	4271 (100%)	0	179 (4%)	0
LIPS	4/1996–10/1998	2002	3·1	F80 *vs* placebo	1677	18–80	271 (16%)	202 (12%)	744 (44%)	933 (56%)	142 (8%)	0
HPS	7/1994–5/1997	2002	5·0	S40 *vs* placebo	20 536	40–80	5082 (25%)	5963 (29%)	8510 (41%)	4876 (24%)	8865 (43%)	3161 (15%)
PROSPER	12/1997–5/1999	2002	3·2	P40 *vs* placebo	5804	70–82	3000 (52%)	623 (11%)	776 (13%)	1105 (19%)	1026 (18%)	3254 (56%)
ALLHAT–LLT	3/1994–5/1998	2002	4·8	P40 *vs* usual care	10 355	≥55	5051 (49%)	3638 (35%)	0	1188 (11%)	0	9167 (89%)
ASCOT– LLA	2/1998–5/2000	2003	3·2	A10 *vs* placebo	10 305	40–79	1942 (19%)	2527 (25%)	0	15 (<1%)	1435 (14%)	8860 (86%)
ALERT	6/1996–10/1997	2003	5·1	F40 *vs* placebo	2102	30–75	715 (34%)	396 (19%)	319 (15%)	81 (4%)	241 (11%)	1702 (81%)
CARDS	11/1997–6/2001	2004	3·9	A10 *vs* placebo	2838	40–75	909 (32%)	2838 (100%)	0	9 (<1%)	97 (3%)	2738 (96%)
Total	..	..	4·7	..	90 056	..	21 575 (24%)	18 686 (21%)	28 725 (32%)	13 406 (15%)	13 255 (15%)	41 354 (46%)

4S=Scandinavian Simvastatin Survival Study.[13] WOSCOPS=West of Scotland Coronary Prevention Study.[14] CARE=Cholesterol And Recurrent Events.[15] Post-CABG=Post-Coronary Artery Bypass Graft.[16] AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study.[17] LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease.[18] GISSI Prevention=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.[19] LIPS=Lescol Intervention Prevention Study.[20] HPS=Heart Protection Study.[21] PROSPER=PROspective Study of Pravastatin in the Elderly at Risk.[22] ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[23] ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm.[24] ALERT=Assessment of Lescol in Renal Transplantation.[25] CARDS=Collaborative Atorvastatin Diabetes Study.[26] S=simvastatin. L=lovastatin. P=pravastatin. F=fluvastatin. A=atorvastatin. *Mean duration of follow-up based on survival times within each trial. Overall mean is weighted by trial-specific variances of logrank (o–e) for major vascular events. †All trials included dietary intervention: WOSCOPS, GISSI Prevention, LIPID, 4S, LIPS, and HPS provided dietary advice; AFCAPS/TexCAPS, Post-CABG, CARE, ALLHAT, ALERT, CARDS, and PROSPER used American Heart Association (AHA) Step 1 diet and CARE intensified to Step 2 diet if LDL cholesterol ≥4·5 mmol/L (175 mg/dL). ‡Other CHD includes patients with a history of other symptomatic CHD but excludes those with a history of MI (as already counted in MI column). §Other vascular includes history of intracerebral bleed, transient ischaemic attack, ischaemic stroke, unknown stroke, and peripheral artery disease. ¶None includes individuals without a history of MI, symptomatic CHD, intracerebral bleed, transient ischaemic attack, ischaemic stroke, unknown stroke, or peripheral artery disease.

Table: **Baseline characteristics and eligibility criteria of participating trials**

the first cycle of such meta-analyses, and involves only trials of statins.

Methods

Study eligibility

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, and was published the next year.[11] Properly randomised trials were eligible for inclusion if: (i) the main effect of at least one of the trial interventions was to modify lipid levels; (ii) the trial was unconfounded with respect to this intervention (ie, no other differences in risk factor modification between the relevant treatment groups were intended); and (iii) the trial aimed to recruit at least 1000 participants with treatment duration of at least 2 years.

Prespecified analyses of major outcomes

The principal planned analyses are described in the published protocol.[11] Briefly, the primary meta-analyses were to be of the effects on clinical outcome in each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and are reported as the effects per 1·0 mmol/L (39 mg/dL) reduction in LDL cholesterol. The main prespecified outcomes were all-cause mortality, CHD mortality, and non-CHD mortality. Secondary analyses were to be of effects on CHD death and on major coronary events (defined as non-fatal myocardial infarction [MI] or CHD death) in particular prespecified subgroups, and of effects on stroke, cancer, and vascular procedures. In addition, we have analysed the effects on major vascular events (defined as the combined outcome of major coronary event, non-fatal or fatal stroke, or coronary revascularisation) in different circumstances.

Statistical analysis

For every trial, the logrank Observed-minus-Expected statistic (o–e) and its variance (v) were calculated from the results during every year of follow-up.[12] For an unweighted meta-analysis, these (o–e) values, one from every trial, would be summed to produce a grand total (G), with variance (V) equal to the sum of their separate variances. The value exp (G/V) would then be the overall event rate ratio (with χ^2_{13} for heterogeneity between the effects in different trials equal to $S–G^2/V$, where S is the sum of $[o–e]^2/v$ for each trial). For the main LDL-weighted meta-analyses, let the mean absolute difference in LDL cholesterol (mmol/L) after 1 year between those allocated active treatment and those allocated control in a particular trial be w. The logrank (o–e) for that trial is then multiplied by the weight w, and its variance by w^2, and these weighted values for every trial are then summed to produce a weighted grand total (G_w) and its variance (V_w). The value $\exp(G_w/V_w)$ is then the one-step weighted estimate of the event rate ratio (RR) per 1·0 mmol/L reduction in

LDL cholesterol (with χ^2_{13} for heterogeneity between the effects per mmol in different trials equal to $S–G_w^2/V_w$). In the figures and in the text, summary rate ratios are presented with 95% CI, whilst those derived from secondary or subgroup analyses are 99% CI.

For subgroup analyses, the weighted results were calculated separately in every subgroup and were then compared with standard χ^2 tests for heterogeneity or, where appropriate, for trend. Where many subgroup analyses were to be done (eg, of sex, age, initial blood pressure, etc), the separate χ^2 statistics for each were summed (as were their degrees of freedom) to yield a global test for heterogeneity that can help make allowance for the multiplicity of comparisons.[12]

Role of the funding sources

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For the first cycle of analyses, individual participant data were available from 14 trials of statin therapy (table),[13–26] but not from one other eligible trial.[27] Data were obtained on 90 056 participants, of whom 42 131 (47%) had pre-existing CHD, 21 575 (24%) were women, 18 686 (21%) had a history of diabetes, and 49 689 (55%) had a history of hypertension. The mean pre-treatment LDL cholesterol was 3·79 mmol/L, and ranged from 3·03 mmol/L in CARDS[26] to 4·96 mmol/L in WOSCOPS[14] (webtable 1[28]). Overall in these trials, the weighted average difference in LDL cholesterol at 1 year was 1·09 mmol/L. The weighted mean duration of follow-up among survivors was 4·7 years, and ranged from 2 years in the GISSI Prevention trial[19] to 6 years in the LIPID trial.[18] Details of the design of individual trials are shown in the table and in webtable 1.

Cause-specific mortality

There were a total of 8186 deaths, including 4655 (57%) from vascular causes and 3531 (43%) from non-vascular causes (webtable 2). During the scheduled treatment period, there were 3832 (8·5%) deaths among the 45 054 participants allocated a statin compared with 4354 (9·7%) among the 45 002 controls. This difference represents a 12% proportional reduction in all-cause mortality per mmol/L LDL cholesterol reduction (RR 0·88, 95% CI 0·84–0·91; p<0·0001; figure 1). In an unweighted analysis, a slightly larger mortality reduction of 13% (RR 0·87, 0·84–0·91; p<0·0001) was found, chiefly because the mean LDL cholesterol reduction at 1 year in these trials was 1·09 mmol/L.

The weighted average relative reduction of 12% in all-cause mortality was attributable mainly to the 19% proportional reduction in CHD deaths (1548 [3·4%] statin *vs* 1960 [4·4%] control: RR 0·81, 95% CI 0·76–0·85; p<0·0001) per mmol/L reduction in LDL cholesterol. There were also non-significant reductions in deaths from stroke (RR 0·91, 99% CI 0·74–1·11; p=0·2), from other vascular causes (RR 0·95, 99% CI 0·78–1·16; p=0·5), and from non-vascular causes (RR 0·95, 95% CI 0·90–1·01; p=0·1). Among the non-vascular causes of death, there was no evidence that lowering LDL cholesterol with a statin adversely affected the risk of death from cancer, respiratory disease, trauma, or other or unknown causes (figure 1).

The 19% proportional reduction in CHD death per mmol/L LDL cholesterol reduction translated into 14 (95% CI 9–19) fewer deaths per 1000 among participants with pre-existing CHD, compared with 4 (1–7) fewer per 1000 among participants who did not have pre-existing CHD (see webfigure 1i). The proportional reduction in the risk of CHD death per mmol/L lower LDL cholesterol was similar in all of the prespecified subgroups examined (global heterogeneity p=0·9; see webfigure 2i).

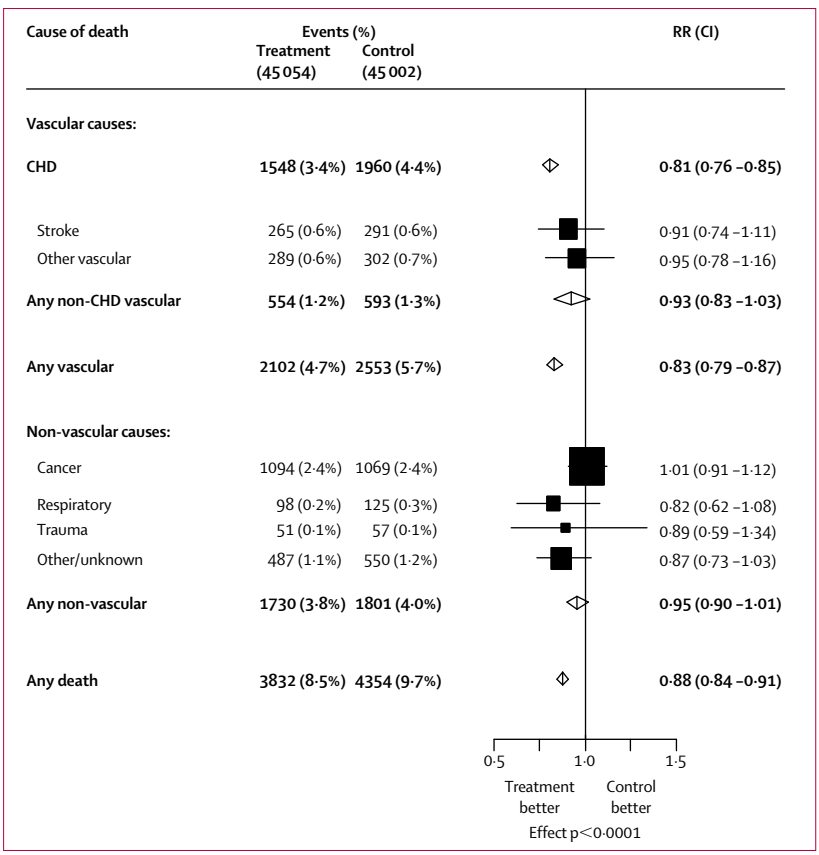

Figure 1: **Proportional effects on cause-specific mortality per mmol/L LDL cholesterol reduction**
Diamonds=totals and subtotals (95%CI). Squares=individual categories (horizontal lines are 99% CIs). Area of square proportional to amount of statistical information in that category. RRs are weighted to represent reduction in rate per 1 mmol/L LDL cholesterol reduction achieved by treatment at 1 year after randomisation. 26 active versus 31 control deaths in the Post-CABG trial could not be subclassified into vascular and non-vascular causes, but were known not to be due to CHD and were assigned to other non-vascular deaths.

See Lancet Online for webtables 1 and 2

See Lancet Online for webfigures 1 and 2

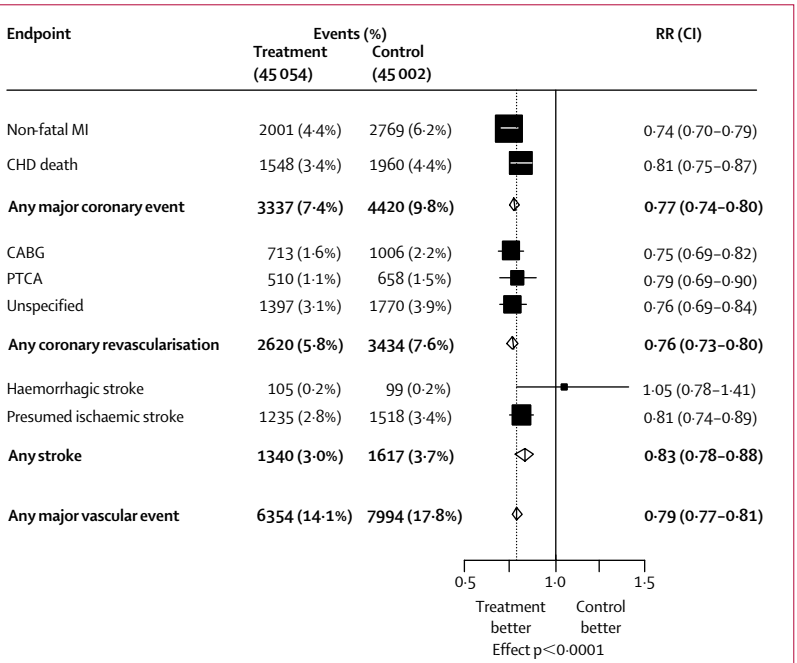

Figure 2: **Proportional effects on major vascular events per mmol/L LDL cholesterol reduction**
Symbols and conventions as in figure 1. Broken vertical line indicates overall RR for any type of major vascular event. CABG=coronary artery bypass graft. PTCA=percutaneous transluminal coronary angioplasty. LIPS only provided data on fatal strokes[20] and so does not contribute to the stroke analyses.

Major coronary events

Data were available on 7757 first major coronary events after randomisation, with 4770 participants having a non-fatal MI and 2987 dying from CHD without having a non-fatal MI (see webtable 2). Overall, there was a highly significant 23% proportional reduction in the incidence of first major coronary events per mmol/L LDL cholesterol reduction (3337 [7·4%] statin *vs* 4420 [9·8%] control: RR 0·77, 95% CI 0·74–0·80; p<0·0001), which included a 26% reduction in non-fatal MI (RR 0·74, 99% CI 0·70–0·79; p<0·0001; figure 2). There was a significant trend (χ^2_1=10·5, p=0·001) towards greater proportional reductions in major coronary events being associated with greater mean absolute LDL cholesterol reductions in the different trials (figure 3 and webfigure 3i), but no significant heterogeneity between the relative effects after weighting for the absolute LDL cholesterol reduction (χ^2_{13}=7·3, p=0·9; webfigure 3i).

See Lancet Online for webfigures 3 and 4

The large number of major coronary events allowed the effects of lowering LDL cholesterol with a statin in different circumstances to be assessed reasonably reliably. Some benefit appeared early after randomisation: even during the first year there was a highly significant 14% proportional reduction in major coronary events (RR 0·86, 99% CI 0·77–0·95; p<0·0001) per mmol/L, and there were highly significant reductions of about 20–30% in every separate year thereafter (all p<0·0001; figure 4). Taking all years together, the overall incidence of major coronary events was reduced by about one quarter per mmol/L reduction in LDL cholesterol among participants with a previous history of MI or other CHD, as well as among those without any pre-existing CHD (figure 5). But since the absolute risk of events was higher among participants with pre-existing CHD, this reduction of about a quarter per mmol/L LDL cholesterol reduction translated into 30 (95% CI 24–37) fewer such participants having major coronary events per 1000 during an average of 5 years, compared with 18 (14–23) fewer among participants who did not have pre-existing CHD (figure 6 and webfigure 1ii).

The proportional reduction in the incidence of major coronary events per mmol/L LDL cholesterol reduction was also about one quarter in all of the other prespecified subgroups (global test for heterogeneity p=0·4; figure 5). Indeed, separately significant reductions in major coronary events were noted within all of these subgroups of baseline characteristics, including: those aged older than 65 years; women; those treated for hypertension; those with a diastolic blood pressure above 90 mm Hg; and those with a history of diabetes (all p<0·0001). In addition to the prespecified subgroups in figure 5, there were significant reductions in major coronary events in other subgroups of interest, including: individuals with pretreatment LDL cholesterol of 2·6 mmol/L or less (200 [6·0%] statin *vs* 247 [7·4%] control; RR 0·75, 99% CI 0·56–1·01; p=0·01); diabetic individuals without pre-existing vascular disease (368 [5·4%] *vs* 475 [7·1%]; RR 0·74, 99% CI 0·62–0·88; p<0·0001); and people aged 75 years or older when randomised (385 [10·6%] *vs* 470 [12·8%]; RR 0·82, 99% CI 0·70–0·96; p=0·002).

Coronary revascularisation

Data were available on 6054 first coronary revascularisation procedures after randomisation (webtable 2). Overall, there was a significant 24% proportional reduction in the incidence of first coronary revascularisation (RR 0·76, 95% CI 0·73–0·80; p<0·0001) per mmol/L LDL cholesterol reduction, with similar proportional reductions in coronary artery grafting and angioplasty (figure 2). There was a significant trend (χ^2_1=13·7, p=0·0002) towards greater proportional reductions in coronary revascularisation being associated with greater mean absolute LDL cholesterol reductions in the different trials (webfigures 3ii and 4i), but no significant heterogeneity between the relative effects after weighting for the absolute LDL cholesterol reduction (webfigure 3ii).

The effect on coronary revascularisations of lowering LDL cholesterol with a statin did not reach significance during the first year after randomisation (RR 0·95, 99% CI 0·84–1·08; p=0·2), but there were clearly significant yearly reductions of between about 25% and

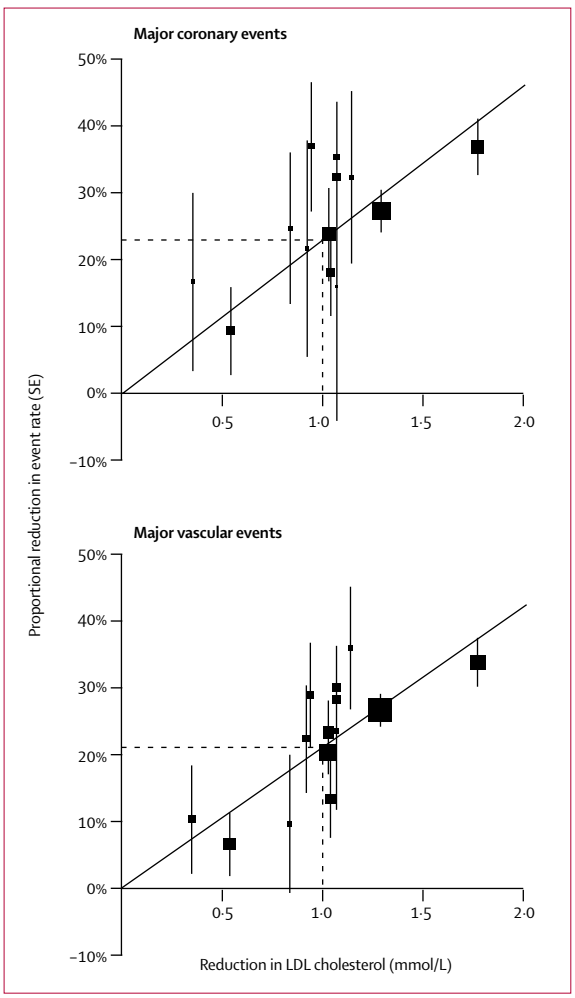

Figure 3: **Relation between proportional reduction in incidence of major coronary events and major vascular events and mean absolute LDL cholesterol reduction at 1 year**

Square represents a single trial plotted against mean absolute LDL cholesterol reduction at 1 year, with vertical lines above and below corresponding to one SE of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL cholesterol difference at 1 year (webtable 1). For each outcome, regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/L LDL cholesterol reduction.

Endpoint	Events (%) Treatment (45 054)	Control (45 002)	RR (CI)
Year 0–1:			
Major coronary event	805 (1·8%)	980 (2·2%)	0·86 (0·77–0·95)
Coronary revascularisation	795 (1·8%)	841 (1·9%)	0·95 (0·84–1·08)
Stroke	297 (0·7%)	311 (0·7%)	0·96 (0·79–1·17)
Major vascular event	**1747 (3·9%)**	**1951 (4·3%)**	**0·90 (0·85–0·96)**
Year 1–2:			
Major coronary event	653 (1·5%)	856 (2·0%)	0·78 (0·70–0·87)
Coronary revascularisation	488 (1·1%)	653 (1·5%)	0·76 (0·66–0·87)
Stroke	264 (0·6%)	363 (0·8%)	0·75 (0·62–0·90)
Major vascular event	**1231 (2·9%)**	**1603 (3·8%)**	**0·78 (0·73–0·83)**
Year 2–3:			
Major coronary event	611 (1·5%)	883 (2·1%)	0·69 (0·61–0·77)
Coronary revascularisation	442 (1·1%)	623 (1·5%)	0·73 (0·64–0·84)
Stroke	274 (0·7%)	327 (0·8%)	0·83 (0·69–1·00)
Major vascular event	**1151 (2·8%)**	**1543 (3·9%)**	**0·74 (0·69–0·79)**
Year 3–4:			
Major coronary event	515 (1·4%)	733 (2·0%)	0·72 (0·64–0·82)
Coronary revascularisation	375 (1·0%)	581 (1·6%)	0·66 (0·57–0·76)
Stroke	221 (0·6%)	298 (0·8%)	0·75 (0·61–0·92)
Major vascular event	**946 (2·6%)**	**1306 (3·8%)**	**0·72 (0·67–0·78)**
Year 4–5:			
Major coronary event	479 (1·6%)	588 (2·1%)	0·81 (0·71–0·92)
Coronary revascularisation	317 (1·1%)	464 (1·7%)	0·70 (0·60–0·82)
Stroke	185 (0·6%)	199 (0·7%)	0·90 (0·72–1·12)
Major vascular event	**811 (2·9%)**	**993 (3·7%)**	**0·79 (0·74–0·86)**
Year 5+:			
Major coronary event	274 (1·5%)	380 (2·2%)	0·71 (0·59–0·84)
Coronary revascularisation	203 (1·2%)	272 (1·6%)	0·73 (0·59–0·90)
Stroke	99 (0·5%)	119 (0·7%)	0·79 (0·57–1·10)
Major vascular event	**468 (2·8%)**	**598 (3·8%)**	**0·74 (0·67–0·82)**

Trend test for major vascular events: χ^2_1=13·9; p=0·0002

0·5 Treatment better 1·0 Control better 1·5

Figure 4: **Proportional effects on major vascular events per mmol/L LDL cholesterol reduction by year**

Symbols and conventions as in figure 1. For each time period, RRs weighted by trial-specific LDL cholesterol reductions at 1 year relate to participants at risk of a first events (as do percentages).

30% during each of the subsequent 5 years (all p<0·001; figure 4). During an average of 5 years of treatment, the reduction in the overall incidence of coronary revascularisation of about one quarter per mmol/L LDL cholesterol reduction translated into 27 (95% CI 20–34) fewer participants having such procedures per 1000 among those with pre-existing CHD at baseline, compared with 12 (9–16) fewer among participants with no such history (figure 6 and webfigure 1iii). The proportional reduction in the incidence of coronary revascularisation procedures per mmol/L LDL cholesterol reduction was about one quarter in all of the prespecified subgroups (global heterogeneity p=0·9; webfigure 2ii).

Stroke

Data were available on a total of 2957 first strokes after randomisation (webtable 2). There were 2282 strokes among 65 138 participants in nine trials[13,15,17–19,21,22,24,26] that sought information on stroke type, of which 204 (9%) were attributed definitely to haemorrhage, 1565 (69%) were confirmed to be ischaemic, and 513 (22%) were of unknown type. Overall, there was a significant 17% proportional reduction in the incidence of first stroke of any type (1340 [3·0%] statin *vs* 1617 [3·7%] control; RR 0·83, 95% CI 0·78–0·88; p<0·0001) per mmol/L lower LDL cholesterol (figure 2). As was the case for major coronary events and revascularisations, there was a significant trend (χ^2_1=6·8, p=0·009) towards greater

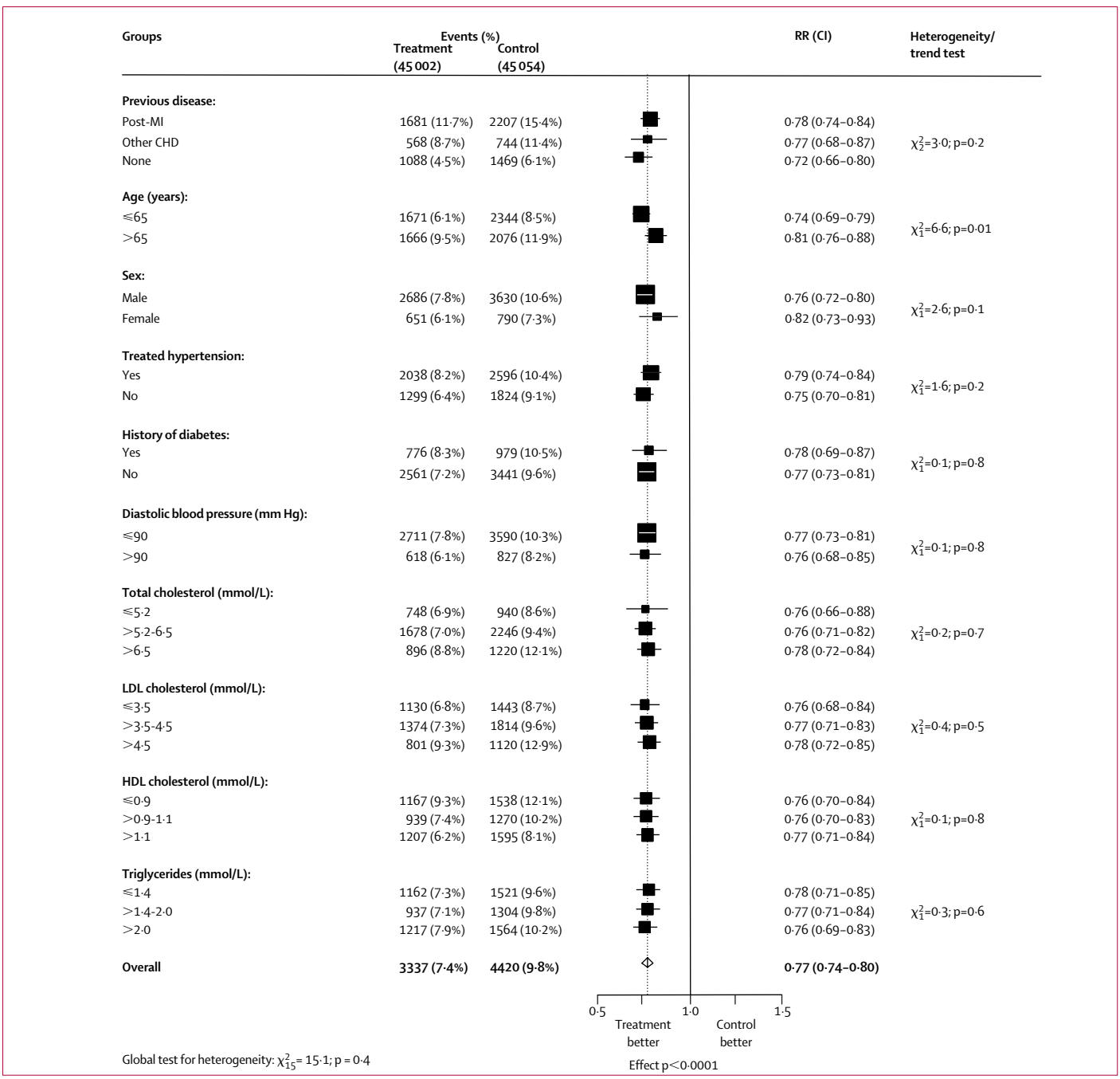

Figure 5: **Proportional effects on major coronary events per mmol/L LDL cholesterol reduction subdivided by baseline prognostic factors**
Symbols and conventions as in figure 1.

proportional reductions in stroke being associated with greater mean absolute LDL cholesterol reductions in the different trials (webfigures 3iii and 4ii).

This overall reduction in stroke reflected a highly significant 19% proportional reduction (RR 0·81, 99% CI 0·74–0·89; p<0·0001) in strokes not attributed to haemorrhage (ie, presumed ischaemic) per mmol/L LDL cholesterol reduction, and no apparent difference in haemorrhagic stroke (RR 1·05, 99% CI 0·78–1·41; p=0·7; figure 2). The overall reduction in presumed ischaemic stroke reflected a highly significant 22% proportional reduction in confirmed ischaemic stroke (RR 0·78, 99% CI 0·70–0·87; p<0·0001) per mmol/L LDL cholesterol reduction and a 12% proportional reduction in stroke of unknown type (RR 0·88, 99% CI 0·75–1·02; p=0·03). There was no

significant reduction in stroke during the first year after randomisation (RR 0·96, 99% CI 0·79–1·17; p=0·6), but there were significant reductions of about 20–25% during each of the subsequent 3 years and favourable trends thereafter (figure 4). During an average of 5 years of treatment, the reduction in the overall incidence of stroke of about one sixth per mmol/L LDL cholesterol reduction translated into eight (95% CI 4–12) fewer participants having any stroke per 1000 among those with pre-existing CHD at baseline, compared with five (1–8) fewer per 1000 among participants with no such history (figure 6 and webfigure 1iv).

Major vascular events

Data were available on 14 348 first major vascular events after randomisation, with 7757 participants having had a major coronary event, 6054 having had a coronary revascularisation procedure, and 2957 having had a stroke (and some having more than one such event; webtable 2). Overall, there was a highly significant 21% proportional reduction in the incidence of major vascular events (RR 0·79, 95% CI 0·77–0·81; p<0·0001) per mmol/L LDL cholesterol reduction, reflecting the similar proportional reductions in major coronary events, coronary revascularisation procedures, and strokes (figure 2). There was a significant trend (χ^2_1=26·4; p<0·0001) towards greater proportional reductions in major vascular events being associated with greater LDL cholesterol reductions in the different trials (figure 3 and webfigure 3iv), but no significant heterogeneity between the relative effects after weighting for the absolute LDL cholesterol reduction (χ^2_{13}=10·1; p=0·7; webfigure 3iv).

Given the large number of major vascular events, the effects of lowering LDL cholesterol with a statin could be examined particularly reliably in various different circumstances (although analysis of this outcome had not been prespecified). There was a significant 10% proportional reduction (RR 0·90, 95% CI 0·85–0·96; p=0·0006) in major vascular events during the first year after randomisation, and this was followed by highly significant yearly reductions of around one quarter during every subsequent year (all p<0·0001; figure 4). Taking all years together, the overall reduction of about one fifth per mmol/L LDL cholesterol reduction translated into 48 (95% CI 39–57) fewer participants having major vascular events per 1000 among those with pre-existing CHD at baseline, compared with 25 (19–31) fewer per 1000 among participants with no such history (figure 6 and webfigure 1v).

The incidence of major vascular events was reduced by about one fifth per mmol/L LDL cholesterol reduction in every prespecified subgroup (global heterogeneity p=0·5; figure 7), and was significant in all of these subgroups considered separately (all p<0·0001). There were also significant reductions in risk per mmol/L LDL cholesterol reduction in a number of other subgroups, including: individuals with pretreatment LDL cholesterol of 2·6 mmol/L or less (383 [11·5%] *vs* 476 [14·3%]; RR 0·73, 99% CI 0·58–0·90; p=0·0001) or even of 2·0 mmol/L or less (75 [10·2%] *vs* 91 [12·9%]; RR 0·66, 99% CI 0·38–1·14; p=0·05); diabetic individuals without previously known vascular disease (713 [10·4%] *vs* 884 [13·1%]; RR 0·75, 99% CI 0·66–0·86; p<0·0001); and those individuals aged 75 years or older when randomised (612 [16·8%] *vs* 721 [19·7%]; RR 0·82, 99% CI 0·72–0·93; p=0·0001).

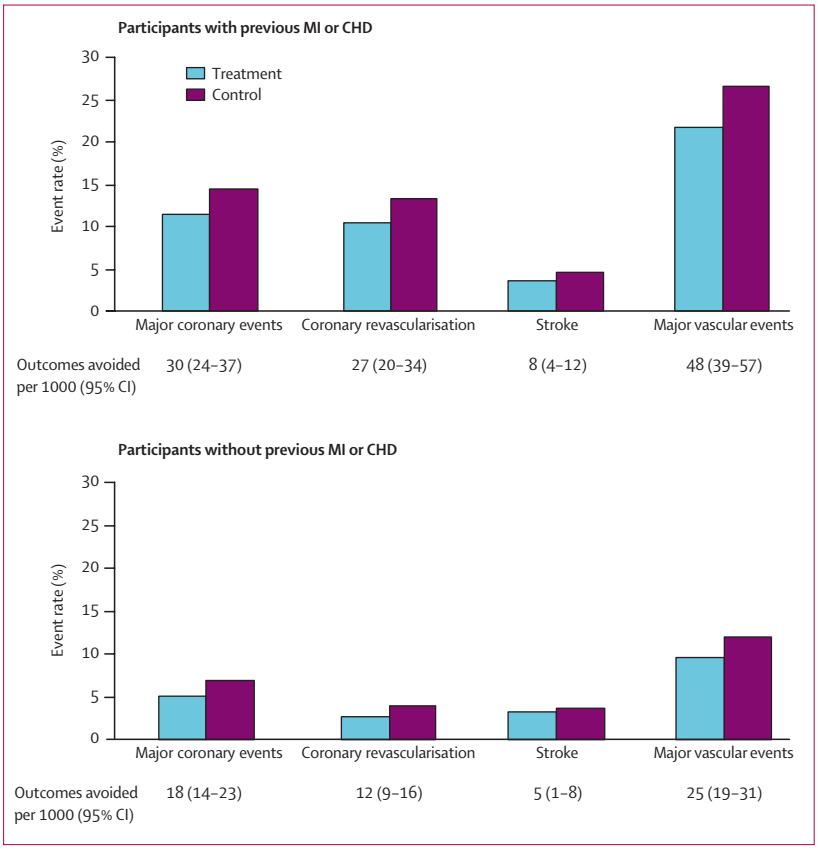

Figure 6: **5-year absolute benefits on particular vascular outcomes per mmol/L LDL cholesterol reduction in participants with and without previous MI or CHD**
Many participants had more than one type of outcome, so sum of absolute differences for separate outcomes exceeds total number of participants avoiding at least one major vascular event.

Cancer

The present analyses are of the 5103 first incident cancers recorded after randomisation, excluding non-fatal recurrences of previously diagnosed cancers, but including any deaths from such recurrences. Non-melanoma skin cancers were not recorded routinely in these trials, and so are not included in the analyses. Overall, there was no evidence that lowering LDL

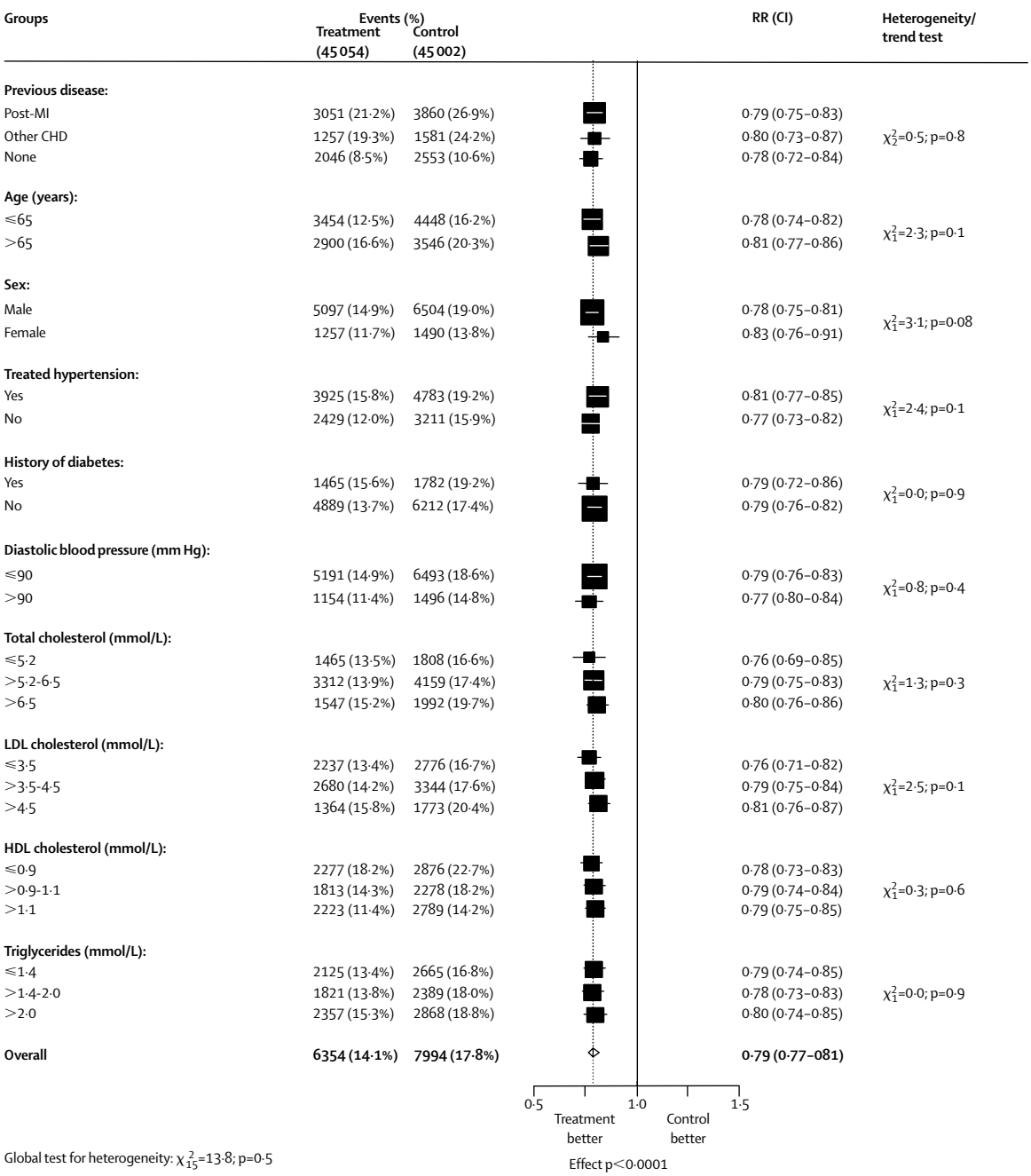

Figure 7: **Proportional effects on major vascular events per mmol/L LDL cholesterol reduction subdivided by baseline prognostic factors**
Symbols and conventions as in figure 1.

cholesterol by 1·0 mmol/L with statin therapy increased the risk of developing cancer (RR 1·00, 95% CI 0·95–1·06; p=0·9; figure 8), and the results of unweighted analyses were similar (webfigure 3v). Furthermore, there was no evidence of an excess incidence of cancer emerging with increasing duration of treatment (χ^2_1 for trend=0·6; p=0·4; figure 9). Moreover, when cancer was analysed by site, there were no apparent excesses among any particular site-specific cancer (figure 8).

Rhabdomyolysis

Information on rhabdomyolysis was available from all but one[23] of the 14 trials (9 [0·023%] of 39 884 patients allocated statin *vs* 6 [0·015%] of 39 817 allocated control), and the 5-year excess risk with statin was small

and not significant (absolute excess 0·01% [SE 0·01]; p=0·4).

Discussion

The main objective of this collaboration is to provide reliable assessments of the major benefits and risks of lipid-modifying treatments, and this first cycle of meta-analyses has specifically addressed the effects of lowering LDL cholesterol with statins. We aimed to minimise both systematic and random errors by bringing together individual participant data from all eligible large randomised trials comparing statin therapy versus control, and by prespecifying the main analyses.[11] Furthermore, by weighting the results in individual trials and subgroups by the size of the achieved LDL cholesterol reductions, we were able to adjust for the potential confounding effects of such differences. The results of this meta-analysis help to clarify the relationship between the reductions in LDL cholesterol and the effects on the incidence of different vascular outcomes, the magnitude of the benefits in different circumstances, the time course over which such benefits emerge, and the safety of the statin regimens studied.

Benefit versus LDL cholesterol reduction

The results of this meta-analysis are consistent with there being an approximately linear relationship between the absolute reductions in LDL cholesterol achieved in these trials and the proportional reductions in the incidence of coronary and other major vascular events. This finding is reinforced by those of some direct randomised comparisons of different statin regimens,[29–31] which also indicate that larger LDL cholesterol reductions produce larger reductions in vascular disease risk. (Further evidence will be provided by other such trials that are still ongoing.[32,33]) Overall among the trials included in the present meta-analysis, the difference in LDL cholesterol at 5 years was about 0·8 mmol/L (chiefly reflecting non-compliance with the allocated treatments). The ratio of the average LDL cholesterol difference for the whole study period to the average difference measured at 1 year was therefore about 0·9. Consequently, a reduction in LDL cholesterol of 1 mmol/L that is sustained for 5 years may well produce a proportional reduction in major vascular events of about 23% (rather than the 21% reduction observed in the weighted analysis). In many circumstances, full compliance with available regimens can reduce LDL cholesterol by substantially more than 1 mmol/L,[10] and the present results suggest that such reductions would produce greater effects on vascular outcomes. For example, a reduction of 1·5 mmol/L in LDL cholesterol with sustained statin therapy might well be expected to reduce the incidence of major vascular events by about one third.

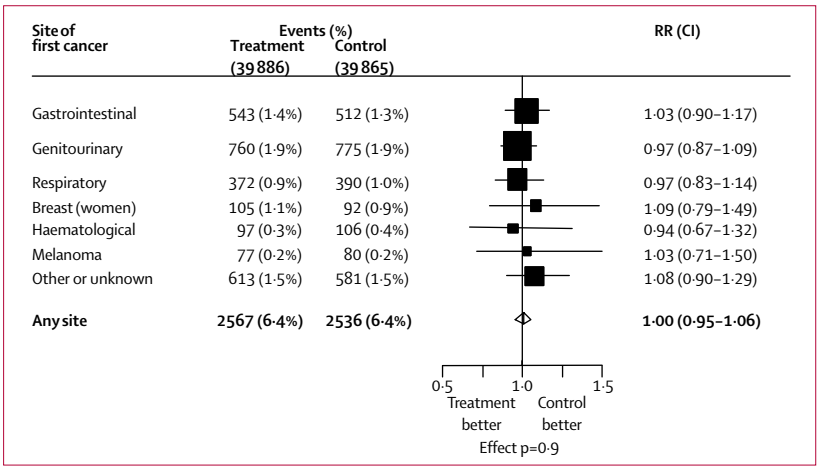

Figure 8: **Proportional effects on cancer incidence per mmol/L LDL cholesterol reduction by site**
Symbols and conventions as in figure 1. For every type of cancer, analyses are of number of participants whose first recorded cancer after randomisation was of that type. ASCOTT-LLA only provided data on fatal cancers[24] and so does not contribute to these analyses.

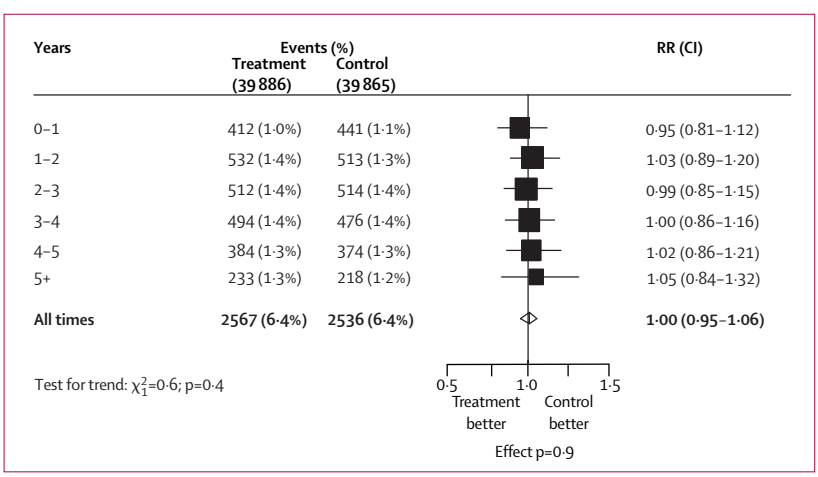

Figure 9: **Proportional effects on cancer incidence per mmol/L LDL cholesterol reduction by year**
Symbols and conventions as in figures 1 and 4. ASCOTT-LLA only provided data on fatal cancers[24] and so does not contribute to these analyses.

Benefits in different subgroups

A wide range of different types of participants was included in the 14 trials that contributed to this meta-analysis, so it was possible to explore the effects of lowering LDL cholesterol with statin therapy in many different subgroups. Weighting these analyses according to the subgroup-specific LDL cholesterol differences between the treatment groups made it possible to allow for any differences between the LDL cholesterol reductions in different subgroups. For example, the absolute reduction in LDL cholesterol with a particular dose of a statin tends to be smaller among those presenting with lower LDL cholesterol levels than among those with higher levels,[21,34] but the proportional reduction in the event rate per mmol/L reduction in LDL cholesterol was largely independent of the presenting level. That is, the results of the present analyses indicate

that while lowering LDL cholesterol from 4 mmol/L to 3 mmol/L reduces the risk of vascular events by about 23%, lowering LDL cholesterol from 3 mmol/L to 2 mmol/L also reduces (residual) risk by about 23%. So, an LDL cholesterol reduction of 2 mmol/L might be expected to reduce risk by as much as 40% (ie, RRs of 0·77×0·77 yielding a combined RR of 0·59). The proportional reductions in major vascular event rates per mmol/L LDL cholesterol reduction were very similar in all of the subgroups examined, including not just individuals presenting with LDL cholesterol below 2·6 mmol/L (100 mg/dL), but other groups for whom there had previously been uncertainty (such as diabetic individuals without pre-existing vascular disease, and people aged older than 75 years).

Evolution of benefits over time

There have been conflicting reports about how rapidly benefits emerge after statin therapy is commenced, with some trials reporting little or no reduction in vascular events within the first year of treatment,[13,15] and one trial[22] reporting no reduction in stroke with 3 years of treatment, whereas other trials have reported more rapid benefits.[29,35] In the present meta-analysis, there was a highly significant 10% proportional reduction in major vascular events per mmol/L LDL cholesterol reduction during the first year (chiefly reflecting the observed 14% proportional reduction in major coronary events) and larger reductions of about 20–30% per mmol/L during every successive year of treatment. There was limited power, however, to assess how early the separate effects on major coronary events, coronary revascularisations, and strokes emerged. The survival analyses showed that the beneficial effects of lowering LDL cholesterol with a statin accumulated during an average of 5 years of treatment, so the absolute benefits increased with continuing treatment. Since this meta-analysis includes only the effects on first events, it underestimates the absolute benefits of continued statin therapy because the incidence of subsequent vascular events has also been shown to be reduced.[36]

Safety of lowering cholesterol

Previously, the results of some observational studies[7,37,38] and early randomised trials[4,5,39,40] had raised concerns that lowering blood cholesterol concentrations might increase the risks of various non-vascular causes of death and of particular cancers (eg, gastrointestinal, respiratory, and haematological). In the present meta-analysis, however, there was no evidence that lowering LDL cholesterol by 1 mmol/L with 5 years of statin therapy increased the risks of any specific non-vascular cause of death or of any specific type of cancer. One of the trials[15] included in the present meta-analysis reported a possible excess risk of breast cancer in women with statin therapy, but this finding was not confirmed in the other contributing trials (RR 1·01, 99% CI 0·73–1·40). Similarly, an apparent excess risk of cancer with statin therapy among people aged older than 70 years in another contributing trial[22] was not confirmed by the findings in the other trials (RR 1·03, 99% CI 0·91–1·16). Conversely, based on the results of non-randomised observational studies, it has been suggested that statin therapy might reduce the incidence of various cancers (including colorectal[41] and prostate cancer[42]), but the results of the present meta-analysis of randomised trials do not support such claims. Although the findings of this meta-analysis provide reassurance that lowering LDL cholesterol with statin therapy does not increase the risk of non-vascular mortality and cancer during an average of 5 years, extended follow-up beyond the study treatment periods (perhaps through national registries) is warranted to identify whether any adverse effects might emerge in the longer term.

Further evidence of the safety of the statin regimens studied is also provided by the extremely low incidence of rhabdomyolysis (5 year excess: 0·01%, SE 0·01). However, none of the trials in the meta-analysis involved a high-dose statin regimen and, since the risk of myopathy is dose-dependent,[43] the possibility that higher doses would result in clinically relevant adverse effects cannot be excluded. Information on episodes of raised liver enzymes was not sought for the meta-analysis, but results of other studies have shown that statins rarely induce hepatitis.[44] In summary, therefore, the potential hazards of lowering LDL cholesterol with these statin regimens seemed to be extremely small in relation to the clear benefits in many circumstances.

Effects on total mortality

Overall among the participants included in this meta-analysis, statin therapy produced a clear reduction in all-cause mortality. Even so, the effects on vascular and non-vascular mortality considered separately may be more widely generalisable to different populations in which the proportions of deaths from such causes differ. Similar proportional reductions in mortality attributed to coronary heart disease and in the incidence of major vascular events were found among a wide range of individuals, while no adverse effect was observed on non-vascular mortality or morbidity in any of the different circumstances studied. So, in populations where the proportion of deaths from occlusive vascular disease is lower than in the meta-analysis, a given proportional reduction in vascular mortality would be expected to translate into a smaller proportional reduction in all-cause mortality. By contrast, in populations at high risk of vascular death (such as individuals with pre-existing occlusive vascular disease), both the proportional and absolute reductions in all-cause mortality would be expected to be larger.

Implications

The results of the present meta-analysis indicate that the proportional reductions in the incidence of major

coronary events, coronary revascularisations, and strokes were approximately related to the absolute reductions in LDL cholesterol achieved with the statin regimens studied, and that the proportional reductions in such major vascular events per mmol/L LDL cholesterol reduction were similar irrespective of the pretreatment cholesterol concentrations or other characteristics (eg, age, sex, or pre-existing disease) of the study participants. Current treatment guidelines are based on lowering LDL cholesterol to particular target levels, with somewhat lower targets for people at higher risk of coronary events.[45,46] The results of this meta-analysis suggest, however, that this strategy may not realise the full potential of such treatment. First, assessment of baseline risk should be based on any type of occlusive vascular event (rather than on coronary events alone), since lowering LDL cholesterol with a statin lowers the risks not just of coronary events but also of revascularisation procedures and of ischaemic strokes. Secondly, treatment goals for statin treatment should aim chiefly to achieve substantial absolute reductions in LDL cholesterol (rather than to achieve particular target levels of LDL cholesterol), since the risk reductions are proportional to the absolute LDL cholesterol reductions. Full compliance with available statin regimens can reduce LDL cholesterol by at least 1·5 mmol/L in many circumstances, and hence might be expected to reduce the incidence of major vascular events by about one third. Ensuring that patients at high 5-year risk of any type of occlusive major vascular event achieve and maintain a substantial reduction in LDL cholesterol would result in major clinical and public-health benefits.

Contributors

All members of the writing committee contributed to the collection and analysis of the data, and to the preparation of the manuscript. All collaborators had an opportunity to contribute to the interpretation of the results and to the drafting of the manuscript. The writing committee accepts full responsibility for the content of this paper.

Conflict of interest statement

Most of the trials in this report were supported by research grants from the pharmaceutical industry. Some members of the writing committee (CB, AK, RP, RC, and JS) have had the costs of participating in scientific meetings reimbursed by the pharmaceutical industry. All other members of the writing committee declare that they have no conflict of interest.

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