Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

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Summary

Background Although statin therapy reduces the risk of occlusive vascular events in people with diabetes mellitus, there is uncertainty about the effects on particular outcomes and whether such effects depend on the type of diabetes, lipid profile, or other factors. We undertook a prospective meta-analysis to help resolve these uncertainties.

Methods We analysed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of a further 71 370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings During a mean follow-up of 4·3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01; p=0·02), which was similar to the 13% reduction in those without diabetes (0·87, 0·82–0·92; p<0·0001). This finding reflected a significant reduction in vascular mortality (0·87, 0·76–1·00; p=0·008) and no effect on non-vascular mortality (0·97, 0·82–1·16; p=0·7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72–0·86; p<0·0001), which was similar to the effect observed in those without diabetes (0·79, 0·76–0·82; p<0·0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69–0·87; p<0·0001), coronary revascularisation (0·75, 0·64–0·88; p<0·0001), and stroke (0·79, 0·67–0·93; p=0·0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.

Interpretation Statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.

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See **Comment** page 94

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Introduction

At least 170 million people worldwide are estimated to have diabetes mellitus, and this number is predicted to more than double by 2030.[1] The rapid rise in prevalence is mainly attributable to an increased incidence of type 2 diabetes. Since both types of diabetes are associated with a substantially increased risk of atherosclerotic vascular disease,[2–4] identification of treatments for the prevention of major occlusive vascular events is a public-health priority.

Both types of diabetes are associated with dyslipidaemia, but the pattern of abnormality differs between them. In type 2 diabetes, triglyceride concentrations are high but HDL cholesterol concentrations tend to be low, whereas in type 1 diabetes triglyceride concentrations are generally lower than those in type 2 diabetes, and HDL cholesterol levels are average or even high.[5] In both diseases, the concentration of LDL cholesterol in the blood is generally similar to the population average, although this apparently benign pattern can mask an increase in atherogenic small dense LDL particles.[6] Observational studies in different populations have shown that a positive log-linear relation exists between blood LDL cholesterol and the risk of coronary heart disease, with this association continuing well below the range of typical cholesterol levels in developed countries.[4,7,8] For example, in around 360 000 men who were screened for the Multiple Risk Factor Intervention Trial (MRFIT),[4] every 1 mmol/L lower blood total cholesterol was associated with about a 50% lower risk of death from coronary heart disease, irrespective of blood cholesterol at baseline. In the 5000 men who had reported a history of diabetes at the baseline assessment for MRFIT, the relation between blood cholesterol and risk of coronary mortality was of similar magnitude, but the absolute risk of coronary mortality was three to five times higher than it was in those without diabetes.[9]

We have previously reported the results of a collaborative meta-analysis of 14 randomised trials of statin therapy (the Cholesterol Treatment Trialists' [CTT] Collaboration).[10] Our results showed that lowering LDL cholesterol by 1 mmol/L reduces the risk of major vascular events (defined as the composite outcome of myocardial infarction or coronary death, stroke, or coronary revascularisation) by about a fifth in a wide range of high-risk participants, largely irrespective of baseline lipid profile or other presenting characteristics, including diabetes. However, there are still some uncertainties about the effects of statins in people with diabetes. For example, there is little information about

	Diabetes mellitus			No diabetes
	Type 1	Type 2*	Any type	
4S[15]	24 (0·5%)	178 (4·0%)	202 (4·5%)	4242 (95·5%)
WOSCOPS[16]	8 (0·1%)	68 (1·0%)	76 (1·2%)	6519 (98·8%)
CARE[17]	193 (4·6%)	393 (9·4%)	586 (14·1%)	3573 (85·9%)
Post-CABG[18]	27 (2·0%)	89 (6·6%)	116 (8·6%)	1235 (91·4%)
AFCAPS/TexCAPS[19]	0	155 (2·3%)	155 (2·3%)	6450 (97·7%)
LIPID[20]	106 (1·2%)	676 (7·5%)	782 (8·7%)	8232 (91·3%)
GISSI-P[21]	120 (2·8%)	462 (10·8%)	582 (13·6%)	3689 (86·4%)
LIPS[22]	39 (2·3%)	163 (9·7%)	202 (12·0%)	1475 (88·0%)
HPS[23]	615 (3·0%)	5348 (26·0%)	5963 (29·0%)	14 573 (71·0%)
PROSPER[24]	51 (0·9%)	572 (9·9%)	623 (10·7%)	5181 (89·3%)
ALLHAT – LLT[25]	0	3638 (35·1%)	3638 (35·1%)	6717 (64·9%)
ASCOT – LLA[26]	0	2527 (24·5%)	2527 (24·5%)	7778 (75·5%)
ALERT[27]	280 (13·3%)	116 (5·5%)	396 (18·8%)	1706 (81·2%)
CARDS[28]	3 (0·1%)	2835 (99·9%)	2838 (100%)	0
Total	1466 (1·6%)	17 220 (19·1%)	18 686 (20·7%)	71 370 (79·3%)

Data are number (%). *Includes 13 participants with diabetes of unknown type.

Table 1: **Number of participants with diabetes by trial**

	Diabetes mellitus			No diabetes (n=71 370)
	Type 1 (n=1466)	Type 2 (n=17 220)*	Any type (n=18 686)	
Age (years)	55·1 (10·7)	63·8 (8·4)	63·1 (8·9)	61·8 (9·5)
Men	985 (67%)	11 536 (67%)	12 521 (67%)	55 960 (78%)
Smokers	314 (21%)	2750 (16%)	3064 (16%)	16 106 (23%)
Vascular disease				
Previous myocardial infarction/CHD	700 (48%)	4429 (26%)	5129 (27%)	37 004 (52%)
Stroke	69 (5%)	866 (5%)	935 (5%)	4236 (6%)
Peripheral arterial disease†	254 (17%)	1903 (11%)	2157 (12%)	7204 (10%)
Any	827 (56%)	6129 (36%)	6956 (37%)	42 647 (60%)
None	639 (44%)	11 091 (64%)	11 730 (63%)	28 723 (40%)
Treated hypertension	698 (48%)	11 887 (69%)	12 585 (67%)	37 104 (52%)
Systolic BP (mm Hg)	140·9 (21·9)	148·6 (20·9)	148·0 (21·1)	141·6 (22·0)
Diastolic BP (mm Hg)	78·9 (11·0)	83·7 (11·3)	83·3 (11·4)	83·0 (11·8)
Body-mass index (kg/m^2)‡	26·2 (4·3)	29·6 (13·6)	29·3 (13·2)	27·1 (4·2)
Total cholesterol (mmol/L)	5·7 (1·0)	5·6 (0·9)	5·6 (0·9)	5·9 (0·9)
LDL cholesterol (mmol/L)	3·4 (0·9)	3·4 (0·8)	3·4 (0·8)	3·9 (0·8)
HDL cholesterol (mmol/L)	1·3 (0·4)	1·2 (0·4)	1·2 (0·4)	1·1 (0·3)
Triglycerides (mmol/L)	1·6 (1·0)	2·1 (1·3)	2·0 (1·2)	1·8 (0·9)
Creatinine (μmol/L)§	101·1 (35·0)	93·6 (22·1)	94·2 (23·5)	98·3 (23·5)

Data are mean (SD) or number (%). CHD=coronary heart disease. BP=blood pressure. *Includes 13 participants with diabetes of unknown type. †Data for peripheral arterial disease missing entirely for Post-CABG[18] and ALLHAT[25] trials. ‡Data for body-mass index missing entirely for Post-CABG trial.[18] §Data for creatinine missing entirely for AFCAPS/TexCAPS trial.[19]

Table 2: **Baseline characteristics of participants presenting with or without diabetes**

the separate effects on major coronary events (ie, myocardial infarction or death from coronary heart disease), on stroke, and on the need for coronary revascularisation. Moreover, whether the benefits of statin therapy are worthwhile in people with diabetes who do not have any history of occlusive vascular disease is unknown. To resolve these uncertainties, we undertook prespecified analyses in the 18 686 participants with diabetes in the 14 statin trials contributing to the CTT meta-analysis.

Methods

Study design

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 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 lasting at least 2 years. The principal planned analyses, as prespecified in the published protocol,[11] have been reported previously. The primary meta-analyses were of the effects on clinical outcomes with each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and were reported as the effects per 1·0 mmol/L reduction in LDL cholesterol. Since many fewer outcomes were available for analysis in individuals with diabetes, we examined possible variation in the proportional effects of allocation to a statin in different circumstances only for major vascular events. Trial participants were considered to have diabetes if they had a recorded history of diabetes at randomisation, and subdivision of diabetes type was done according to the definitions used in the individual trials. We did not collect information about new diagnoses of diabetes occurring after randomisation.

Statistical analysis

For every trial, the log rank observed minus expected statistic (o–e) and its variance (v) were calculated from the results during each year of follow-up.[12] For the main LDL-weighted meta-analyses, w is the mean absolute difference in LDL cholesterol (mmol/L) after 1 year between participants allocated active treatment and those allocated control in a particular trial. The log rank (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_{n-1} for heterogeneity between the effects per mmol/L in n different trials equal to $S–G_w^2/V_w$, where S is the sum of the $[o–e]^2/v$ for every trial). To help make allowance for repeated subdivision of the data (into people with or without diabetes at baseline, and then again into other subcategories of those with diabetes), only summary rate ratios are presented with 95% CIs; all other rate ratios are presented with 99% CIs.

For subgroup analyses, we used the categories which had been prespecified in the original meta-analysis

protocol,[11] together with three new subgroups. These new subgroups categorised participants according to (i) LDL/HDL ratio; (ii) estimated glomerular filtration rate, as calculated from the simplified Modification of Diet in Renal Disease (MDRD) study formula;[13,14] and (iii) predicted yearly risk of a major vascular event, which was calculated with a Poisson model incorporating baseline characteristics of the control group (for further details see webappendix).

In the analysis of prognostic subgroups we chose thresholds of risk that defined three risk categories with roughly similar numbers of major vascular events. Life-table methods were used to estimate the absolute effects of treatment at 5 years.

Role of the funding source

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

Results

Individual participant data were available from 14 trials of statin therapy (table 1).[15–28] Overall, diabetes was reported in 18 686 participants at trial entry, most of whom had type 2 diabetes; the remaining 71 370 participants were not known to have diabetes (table 1). Table 2 shows the characteristics of participants with and without diabetes, with subdivision by type of diabetes. Compared to participants without diabetes, the mean differences in plasma LDL cholesterol concentrations at 1 year were similar in those with type 2 diabetes, but were less in those with type 1 diabetes (webtable). The mean duration of follow-up in participants with diabetes was 4·3 years (ranging from 1·9 years in the GISSI Prevention trial[21] to 5·6 years in the AFCAPS/TexCAPS trial).[19]

Participants with diabetes had a 9% reduction in all-cause mortality (RR 0·91, 99% CI 0·82–1·01; p=0·02) per mmol/L LDL cholesterol reduction, which was similar to the 13% reduction in those without a history of diabetes (0·87, 99% CI 0·82–0·92; p<0·0001; figure 1). In participants with diabetes, there were reductions in mortality due to coronary heart disease (0·88, 99% CI 0·75–1·03; p=0·03) and in all-vascular mortality (0·87, 99% CI 0·76–1·00; p=0·008), and the effects on coronary heart disease and non-coronary heart disease vascular mortality were similar in participants irrespective of whether diabetes was present (figure 1). There was no evidence that the effects on non-vascular mortality differed between participants with or without diabetes (figure 1), nor of an excess risk of non-vascular causes of death in participants with diabetes (0·97, 99% CI 0·82–1·16; p=0·7; figure 1).

Among participants with diabetes, there was a significant 21% proportional reduction (0·79, 99% CI 0·72–0·86; p<0·0001) in the incidence of major vascular events per mmol/L LDL cholesterol reduction, which was similar to the 21% reduction per mmol/L LDL cholesterol reduction in those without diabetes (0·79, 99% CI 0·76–0·82; p<0·0001; figure 2). There were also significant reductions in major coronary events (0·78, 99% CI 0·69–0·87; p<0·0001), coronary revascularisation (0·75, 99% CI 0·64–0·88; p<0·0001), and stroke (0·79, 99% CI 0·67–0·93; p=0·0002) in participants with diabetes, and the effect on each outcome was similar in participants irrespective of whether or not they had diabetes (figure 2).

The large number of major vascular events (n=3247) in people with diabetes allowed the effects of lowering LDL cholesterol with a statin to be assessed in several subgroups. Among people with diabetes, the proportional reduction of about a fifth in major vascular events per mmol/L LDL cholesterol reduction was much the same

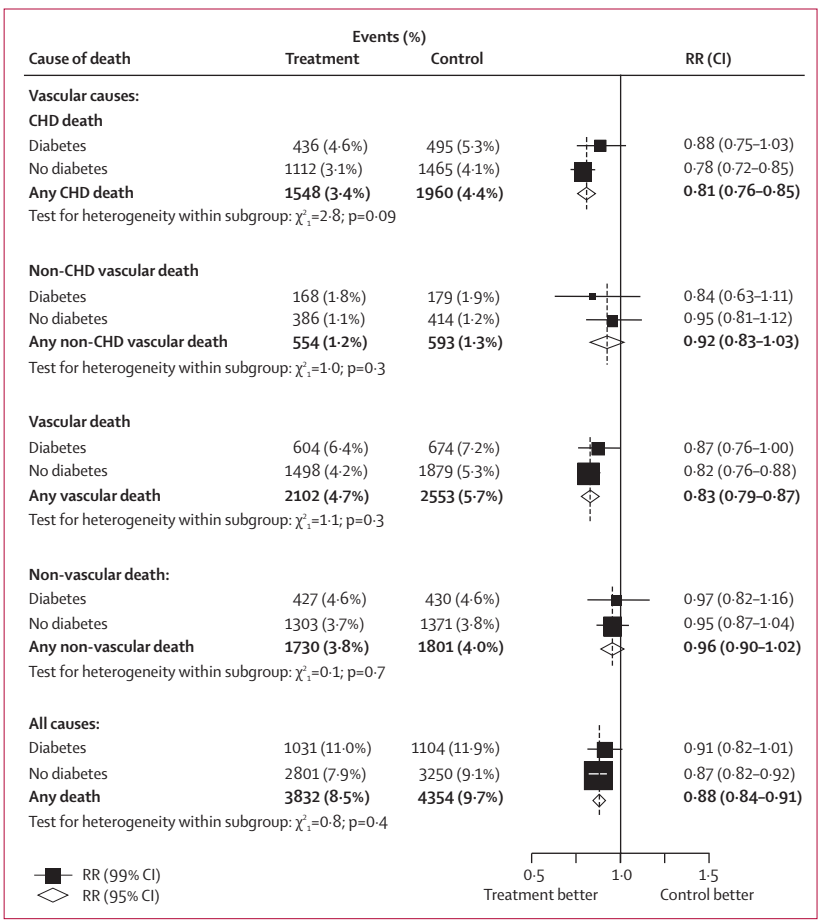

Figure 1: **Proportional effects on cause-specific mortality per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**

Rate ratios (RRs) are plotted comparing outcome in participants who were allocated statin treatment to that in those allocated control, along with their CIs. The area of each square is proportional to the amount of statistical information in that particular category. Diamonds or squares to the left of the solid line indicate benefit with treatment, but this is significant (ie, p<0·05 and p<0·01, respectively) only if the diamond or horizontal line does not overlap the solid line. The RRs are weighted to represent the reduction in the rate per 1 mmol/L LDL cholesterol reduction achieved by treatment at 1 year after randomisation.

See **Online** for webappendix and webtable

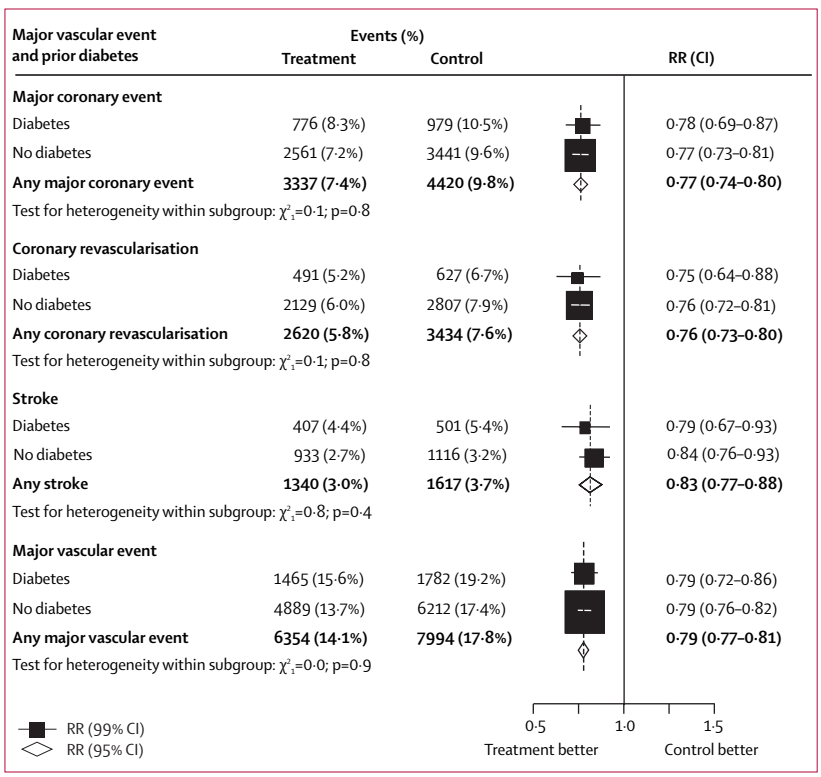

Figure 2: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**
Symbols and conventions as in figure 1.

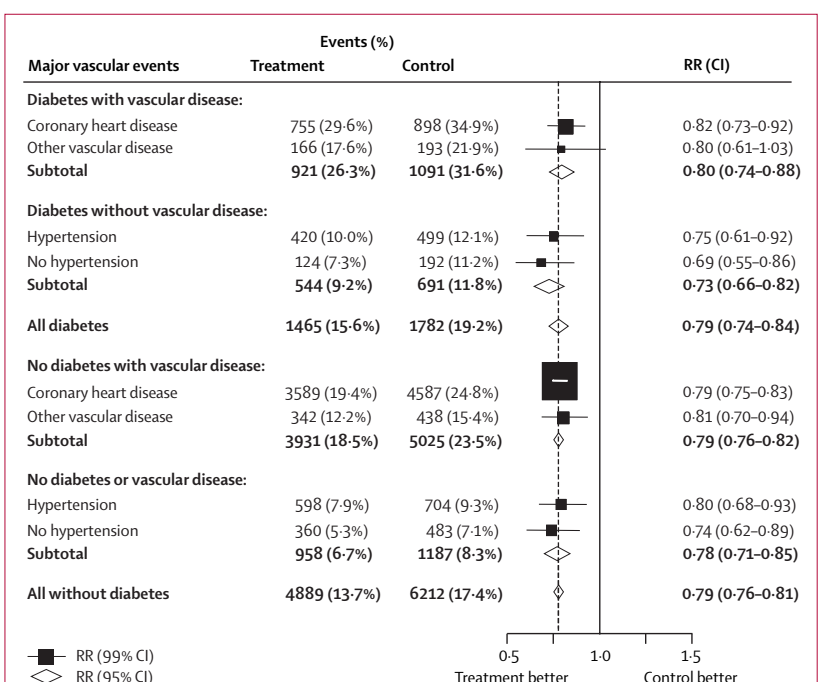

Figure 3: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants with and without diabetes by history of vascular disease**
Symbols and conventions as in figure 1. Vascular disease corresponds to a previous history of coronary heart disease, cerebrovascular disease, or peripheral arterial disease.

irrespective of whether vascular disease (ie, coronary, cerebrovascular, or peripheral arterial) was present (0·80, 95% CI 0·74–0·88 with vascular disease; 0·73, 95% CI 0·66–0·82 without vascular disease; figure 3). Among the 6956 individuals with diabetes and a history of vascular disease, the effects of allocation to a statin were similar in those with coronary heart disease (0·82, 99% CI 0·73–0·92; p<0·0001) and those with other types of vascular disease (0·80, 99% CI 0·61–1·03; p=0·02; figure 3). In the 11 730 participants with diabetes and without known vascular disease, the effects were also similar in those with a history of hypertension (0·75, 99% CI 0·61–0·92; p=0·0003) and those without such a history (0·69, 99% CI 0·55–0·86; p<0·0001; figure 3).

The incidence of major vascular events was reduced by about a fifth per mmol/L LDL cholesterol reduction in all prognostic subgroups of participants with diabetes that were examined (figure 4 and figure 5). The proportional effect was similar irrespective of baseline features, including type of diabetes, sex, age, treated hypertension, body-mass index, systolic or diastolic blood pressure, smoking status, and estimated glomerular filtration rate (figure 4). When participants were ranked according to their predicted yearly risk of a major vascular event, the proportional reduction per mmol/L LDL cholesterol reduction was similar in each of the three groups of expected risk (<4·5%, ≥4·5–<8·0%, and ≥8·0% per year). There was some limited direct evidence of benefit in the 1466 people with type 1 diabetes (0·79, 99% CI 0·62–1·01; p=0·01), but in the remaining subgroups the proportional reductions were all clearly significant when considered individually (all p<0·01; figure 4).

The proportional reduction in major vascular events of a fifth per mmol/L LDL cholesterol reduction was similar in people with diabetes in each of the subcategories of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and LDL/HDL ratio considered (global heterogeneity χ^2_{10}=5·6; p=0·8; figure 5). We also did exploratory analyses of the effects of statin therapy in the 9992 individuals with diabetes with initial LDL cholesterol concentrations less than 3·5 mmol/L (webfigure). Although data were sparse, the results were consistent with a reduction of about a fifth per mmol/L LDL cholesterol reduction in major vascular events throughout the range that we studied, at least down to an initial LDL cholesterol of 2·6 mmol/L or less, as was the case for participants without diabetes.

Overall, there was a 10% proportional reduction in major vascular events in year 1 followed by reductions of around 20–30% in successive years, and these proportional reductions were similar for people with or without diabetes (figure 6). Among all participants with diabetes, after 5 years, 42 (95% CI 30–55) fewer people had major vascular events per 1000 allocated statin therapy per mmol/L LDL cholesterol reduction. The absolute benefit was larger among those with known vascular disease at baseline than it was in those without such disease (57 [95% CI 34–80] *vs*

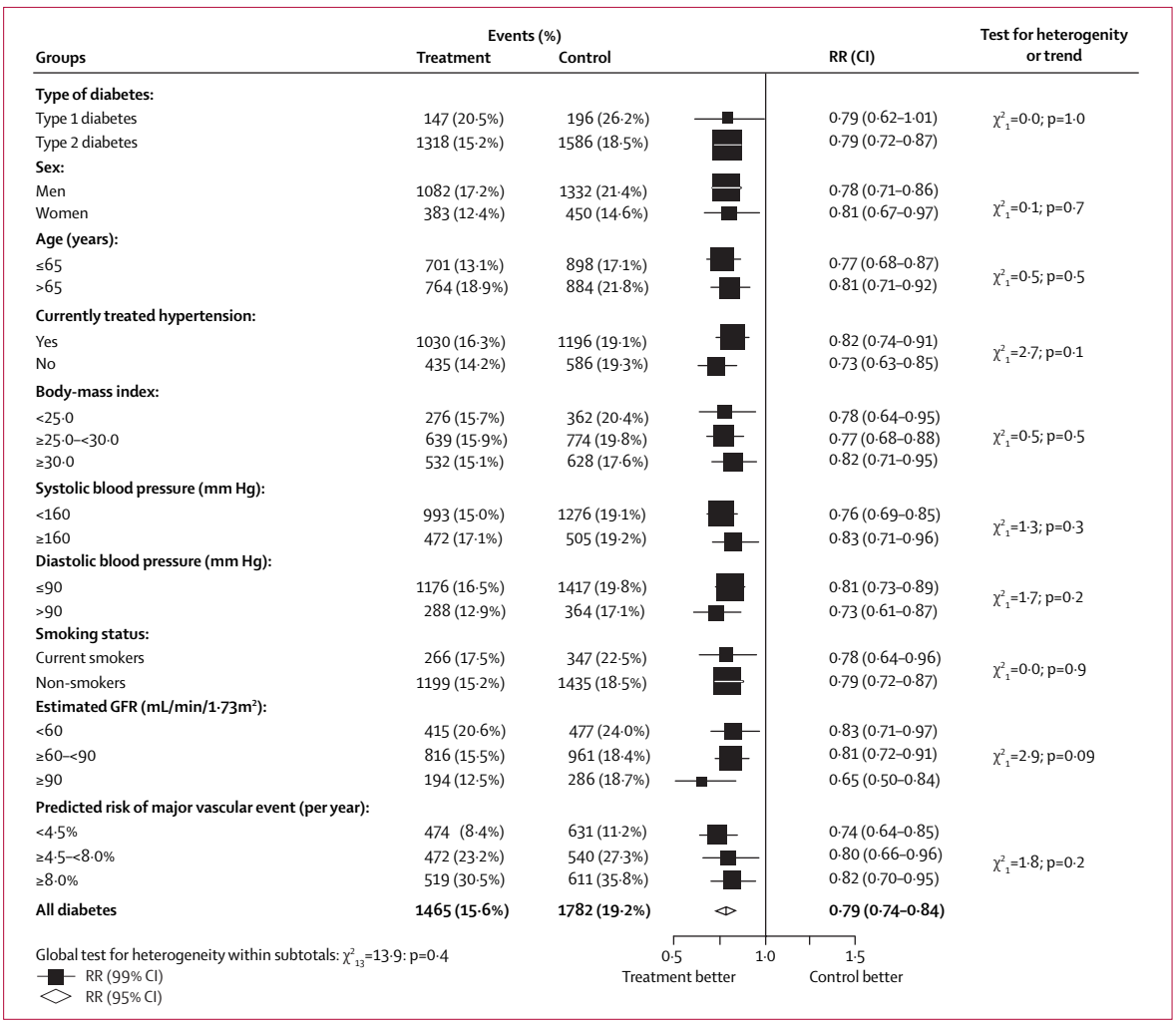

Figure 4: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline prognostic factors in participants with diabetes**
Symbols and conventions as in figure 1. Tests for trend are shown for subgroups involving three categories, heterogeneity tests for those involving two. GFR=glomerular filtration rate.

36 [95% CI 23–49] fewer major vascular events per 1000 per mmol/L LDL cholesterol reduction).

Discussion

The main report of the Cholesterol Treatment Trialists' (CTT) Collaboration showed that statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about a fifth per mmol/L reduction in LDL cholesterol, largely irrespective of initial lipid profile or other baseline characteristics.[10] Larger reductions in LDL cholesterol were associated with greater proportional reductions in major vascular events, which meant that the expected absolute benefit was proportional to the baseline risk of a participant and the absolute reduction in LDL cholesterol achieved by statin therapy.

Several trials have assessed the benefits of statin therapy in people with diabetes, in whom the risks of occlusive vascular events are raised.[28,29] Although these trials showed that statin therapy was effective for the prevention of vascular events in participants with diabetes, our meta-analysis of all available data provides more reliable information about the effects of statin therapy on specific vascular outcomes, and about any possible variation in its effects on major vascular events in particular clinical circumstances.

See Online for webfigure

Among the 14 statin trials that we analysed, the weighted proportional effects of statin therapy on each of the fatal and non-fatal clinical outcomes were similar for participants with or without diabetes. In all diabetic participants, statin therapy reduced the 5-year incidence of major vascular events by about a fifth per mmol/L reduction in LDL cholesterol, with similar proportional reductions in major coronary events, stroke, and the need for coronary revascularisation. Standard doses of a statin reduce LDL cholesterol by about 40%, which translates

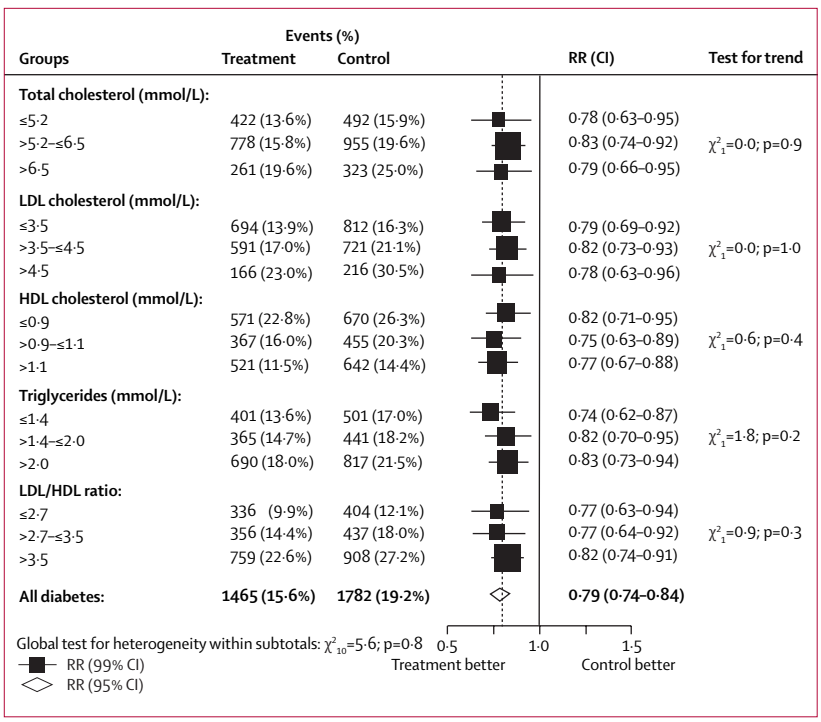

Figure 5: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline lipid profile in participants with diabetes**
Symbols and conventions as in figure 4.

into a reduction of at least 1·5 mmol/L for many people with diabetes, so our results suggest that such an absolute reduction in LDL cholesterol would prevent about a third of patients from having a major vascular event.

Since a wide range of people with diabetes were included in the meta-analysis, we were able to explore the effects of lowering LDL cholesterol with statin therapy in several prognostic subgroups. Weighting these analyses according to the subgroup-specific reductions in LDL cholesterol meant that any differences between subgroups in the size of reductions in LDL cholesterol could be allowed for. Overall, among all participants with diabetes, the proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol was similar irrespective of a previous history of vascular disease, sex, age, treated hypertension, body-mass index, systolic or diastolic blood pressure, smoking history, and estimated glomerular filtration rate. Although the majority of participants in these trials had type 2 diabetes, there was no evidence that the effects of statin therapy on major vascular events in people with type 1 diabetes differed from that in those with type 2 diabetes; indeed, the reduction in major vascular events in people with type 1 diabetes was statistically significant.

Our results showed clearly, in particular, that the proportional benefits on major vascular events in people with diabetes did not depend on sex. Among women and men with diabetes at equivalent risk of major vascular events, therefore, the absolute benefits of statin therapy will probably be similar. (Notwithstanding suggestions to the contrary,[30] this argument applies with equal strength irrespective of whether a person has diabetes: the consistency of the proportional benefit in all subgroups studied in the main CTT report[10] suggests clearly that, in women and men with a comparable risk of occlusive vascular disease, the absolute benefits of statin therapy are likely to be similar. A decision whether to institute treatment with a statin should be determined mainly by an assessment of risk, and not by a person's sex.)

This meta-analysis also showed that the proportional benefit of statin therapy in people with diabetes, after adjustment for the absolute reduction in LDL cholesterol, was largely independent of pretreatment concentrations of LDL cholesterol, HDL cholesterol, and triglycerides. In particular, the proportional benefit did not depend on pretreatment concentrations of LDL cholesterol down to at least 2·6 mmol/L (which corresponds to a concentration of 2 mmol/L or less after treatment). The benefits seemed to be roughly linearly related to the absolute LDL cholesterol reduction produced by statin therapy, without any lower threshold below which benefit was absent. This finding suggests that treatment guidelines which recommend titration of the statin dose to achieve a target LDL cholesterol might need to be reviewed.[31–33]

At present, treatment guidelines generally recommend that statin therapy is considered for people with type 2 diabetes whose future risk of a vascular event exceeds a particular risk threshold—eg, guidelines from the UK National Institute for Health and Clinical Excellence (NICE) recommend statin therapy for all people with diabetes and a history of vascular disease, and for all those without known vascular disease in whom the predicted 10-year risk of a major coronary event or stroke exceeds 20%.[34] Among people with diabetes but no known vascular disease in this meta-analysis, the average risk of a major vascular event was about 2·9% per year, which is equivalent to a yearly risk of about 2·4% of a major coronary event or stroke (the outcome on which NICE guidelines are based, which does not include coronary revascularisation). Therefore, over 10 years the average risk of this outcome in people with diabetes but without vascular disease would exceed the NICE threshold of 20%.

Our meta-analysis has shown that the absolute benefit in participants with diabetes during a mean of 4·3 years of statin therapy was large. However, the absolute risk for people with diabetes in these trials was probably affected by criteria for trial entry, so the observed absolute benefits of statin therapy might not be directly generalisable to an unselected population of people with diabetes. Nevertheless, the consistency of the reduction in major vascular events in the present subgroup analyses suggests that the proportional benefit is probably widely generalisable in other populations with diabetes. Consequently, the absolute benefits in any specific population of patients may be

best estimated by application of a reduction of about a fifth per mmol/L LDL cholesterol reduction to the relevant age-specific and sex-specific rates for that population.

In the meta-analysis of all patients contributing to the first CTT cycle, statin therapy did not increase the risk of non-vascular causes of death or of cancer when used in moderate doses for an average of 5 years, and the present analyses show clearly that there is a similar absence of hazard in the participants with diabetes who were considered separately.[10] Even in aggregate, too few cases of rhabdomyolysis were reported in participants with diabetes for meaningful analyses in this group alone. But, statin therapy was not associated with an increased incidence of rhabdomyolysis in all participants contributing to the first cycle (nine [0·023%] *vs* six [0·015%]; p=0·4).

The original CTT protocol specified that analyses were to be undertaken in discrete cycles, with the trials to be included in each cycle agreed before the results of those trials were known.[11] This strategy was designed to keep to a minimum biases caused by analyses being prompted by publication of particularly positive or negative studies. The 14 trials that were to be included in the first cycle were agreed in 2004, and the main report of analyses was published in 2005.[10]

Recently, two large trials of statin therapy in people with diabetes have been reported: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin Dependent Diabetes Mellitus (ASPEN),[35] and the German Diabetes and Dialysis Study (4D).[36] The ASPEN trial included 2410 people with type 2 diabetes, most of whom had no history of vascular disease, who were randomly assigned to atorvastatin 10 mg daily or placebo; there was a mean reduction in LDL cholesterol of 0·9 mmol/L after about 4 years, and a 10% non-significant reduction (hazard ratio 0·90; 95% CI 0·73–1·12) in the primary outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, resuscitated cardiac arrest, and unstable angina. The 4D trial included 1255 patients with diabetes, all receiving haemodialysis for renal failure, who were randomly assigned to atorvastatin 20 mg daily or placebo; there was a mean reduction in LDL cholesterol of 1·1 mmol/L at 1 year, and a non-significant 8% reduction (hazard ratio 0·92; 95% CI 0·77–1·10) in the primary outcome of myocardial infarction, cardiac death, or stroke.

Since both of these trials reported apparently unpromising results, we considered whether their inclusion would have been likely to change our conclusions. In a combined analysis of data from the present 14 trials and published summary data from the ASPEN and 4D trials, the estimated proportional reduction in major vascular events per mmol/L LDL cholesterol reduction changed only slightly, from 21% to about 20%. Moreover, only the ASPEN trial can provide information about whether or not statins are worthwhile in low-risk individuals with diabetes and no history of vascular disease. Again, addition of the available published data from ASPEN had little effect on the estimated proportional reduction per mmol/L reduction in LDL cholesterol, which changed from 27% to about 25%. Our main conclusions, therefore, are not materially affected by the results of the ASPEN and 4D trials.

In addition to these two trials involving only participants with diabetes, other statin trials published since 2004 (ALLIANCE,[37] SPARCL,[38] and MEGA[39]), and one which could not be included in the first analysis cycle (GREACE),[40] included about 2500 diabetic participants in total. All these trials reported substantial reductions in

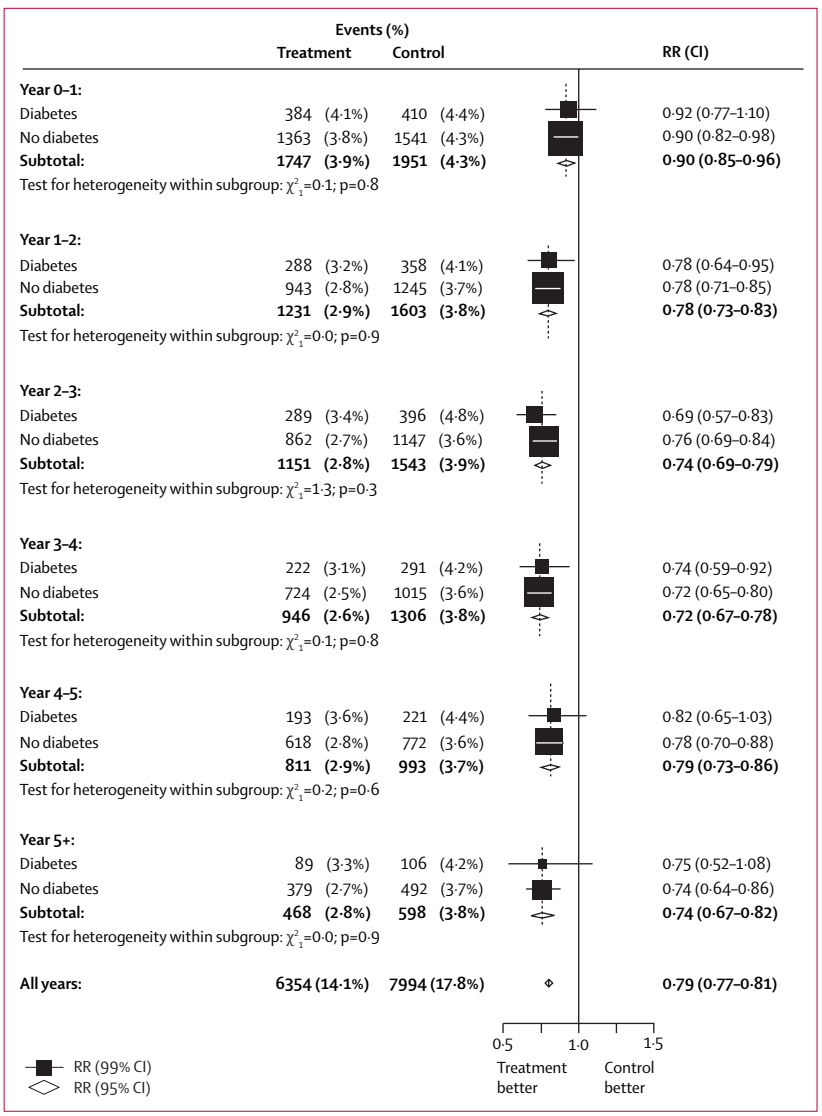

Figure 6: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol, by year, in participants with and without diabetes**

Symbols and conventions as in figure 1. For every time period, rate ratios—weighted by the trial-specific absolute reductions in LDL cholesterol at 1 year—are plotted comparing the proportion of participants at risk with a first event in those allocated statin treatment to the proportion in those allocated to control.

their primary outcomes, and the addition of results from these four trials is unlikely to weaken our conclusions. In particular, only one of these trials was a primary prevention study (MEGA)[39] and, in view of the small numbers of major vascular events occurring in participants with diabetes in this trial, its inclusion would not be expected to modify our conclusions about the effectiveness of statin treatment in people with diabetes without known vascular disease.

This meta-analysis shows convincingly that the proportional benefits of statin therapy on major vascular events were similar in a wide range of individuals with diabetes, including those with no previous history of vascular disease, and benefits were similar to those observed in people without diabetes. Therefore, the cost-effectiveness of treatment for a person at a specific absolute level of risk of major vascular events, irrespective of whether diabetes is present, will be much the same. The Heart Protection Study[41] has shown that a generic statin regimen producing a mean reduction of about 1 mmol/L was cost effective (ie, cost saving or costing less than GBP£2500 per life-year gained) in people who have risks of a major vascular event as low as about 1% per year. This finding suggests that such treatment is likely to be cost effective for almost all people with diabetes. Statin therapy is only likely to be inappropriate when there are compelling reasons to avoid such treatment, such as concerns about safety (eg, in pregnancy) or a low short-term absolute risk of vascular disease (as in type 1 diabetes in children). Since the absolute size of the benefit depends chiefly on the absolute reduction in LDL cholesterol that is achieved, present guidelines might need to be revised to ensure that a statin regimen which is sufficient to produce a substantial reduction in LDL cholesterol is considered for all people with diabetes, irrespective of whether vascular disease has developed and irrespective of lipid profile.

Contributors

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

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Conflict of interest statement

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