

Articles

MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial

Heart Protection Study Collaborative Group*

Summary

Background Individuals with diabetes are at increased risk of cardiovascular morbidity and mortality, although typically their plasma concentrations of LDL cholesterol are similar to those in the general population. Previous evidence about the effects of lowering cholesterol in people with diabetes has been limited, and most diabetic patients do not currently receive cholesterol-lowering therapy despite their increased risk.

Methods 5963 UK adults (aged 40–80 years) known to have diabetes, and an additional 14 573 with occlusive arterial disease (but no diagnosed diabetes), were randomly allocated to receive 40 mg simvastatin daily or matching placebo. Prespecified analyses in these prior disease subcategories, and other relevant subcategories, were of first major coronary event (ie, non-fatal myocardial infarction or coronary death) and of first major vascular event (ie, major coronary event, stroke or revascularisation). Analyses were also conducted of subsequent vascular events during the scheduled treatment period. Comparisons are of all simvastatin-allocated versus all placebo-allocated participants (ie, intention to treat), which yielded an average difference in LDL cholesterol of 1.0 mmol/L (39 mg/dL) during the 5-year treatment period.

Findings Both among the participants who presented with diabetes and among those who did not, there were highly significant reductions of about a quarter in the first event rate for major coronary events, for strokes, and for revascularisations. For the first occurrence of any of these major vascular events among participants with diabetes, there was a definite 22% (95% CI 13–30) reduction in the event rate (601 [20.2%] simvastatin-allocated vs 748 [25.1%] placebo-allocated, $p < 0.0001$), which was similar to that among the other high-risk individuals studied. There were also highly significant reductions of 33% (95% CI 17–46, $p = 0.0003$) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95% CI 13–40, $p = 0.0007$) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L (116 mg/dL). The proportional reduction in risk was also about a quarter among various other subcategories of diabetic patient studied, including: those with different duration, type, or control of diabetes; those aged over 65 years at entry or with hypertension; and those with total cholesterol below 5.0 mmol/L (193 mg/dL). In addition, among participants who had a first major vascular event following randomisation, allocation to simvastatin reduced the rate of subsequent events during the scheduled treatment period.

*Collaborators and participating hospitals are listed on *The Lancet* website (<http://image.thelancet.com/extras/O3art3418webappendix.pdf>)

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Interpretation The present study provides direct evidence that cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients studied. After making allowance for non-compliance, actual use of this statin regimen would probably reduce these rates by about a third. For example, among the type of diabetic patient studied without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event (and, among these 45 people, to prevent about 70 first or subsequent events during this treatment period). Statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.

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Introduction

Diabetes mellitus contributes substantially to the global burden of disease, with an estimated 150 million people affected worldwide, and its prevalence is expected to double by 2025.¹ Myocardial infarction and stroke are common causes of major morbidity in people with diabetes, most of whose deaths are attributed to cardiovascular causes.^{2–4} In type 2 diabetes, blood triglyceride concentrations tend to be elevated and HDL cholesterol concentrations reduced even with good metabolic control, whereas a similar pattern tends to emerge in type 1 diabetes mellitus only when glycaemic control is poor.^{5,6} Typically in both type 1 and type 2 diabetes, however, blood concentrations of total and LDL cholesterol are similar to those in the general population. Perhaps as a consequence, most people with diabetes do not receive cholesterol-lowering therapy despite their elevated risk, apart from those who have marked dyslipidaemia or pre-existing coronary heart disease.^{7,8} Instead, the focus in diabetes has tended to be on the control of blood glucose and of blood pressure.^{9,10}

Observational studies in different populations indicate a continuous positive relationship between coronary disease risk and blood LDL cholesterol concentration that extends well below the range commonly seen in Western populations, without any definite threshold below which a lower concentration is not associated with lower risk.^{11–15} This relationship is approximately linear when coronary disease risk is plotted on a logarithmic (or doubling) scale, which implies that the proportional reduction in risk associated with a given absolute difference in LDL cholesterol concentration is similar throughout the range that has been studied. For example, among 360 000 middle-aged American men screened for the Multiple Risk Factor Intervention Trial (MRFIT),¹² a prolonged 1.0 mmol/L lower blood total cholesterol was

associated with about a 50% lower coronary disease risk, regardless of the baseline cholesterol concentration. This association was of similar relative strength among the 5000 men in that study who had diabetes at baseline and among the remainder who did not, but the absolute risk of coronary mortality at each level of blood cholesterol was three to five times higher in the presence of diabetes. More recently, the United Kingdom Prospective Diabetes Study (UKPDS)¹⁶ has provided further evidence of a similar direct, and continuous, association of coronary disease risk with LDL cholesterol concentration among about 3000 individuals with type 2 diabetes.

Despite the increased risk of macrovascular complications in people with diabetes, relatively few had been studied in previous randomised trials of cholesterol-lowering statin therapy. A total of only about 1500 patients with pre-existing coronary disease who were included in those trials also had diabetes (predominantly type 2),¹⁷⁻²⁰ and subgroup analyses suggested that the proportional effect on coronary disease risk among them was similar to that observed among the other patients studied.²⁰⁻²³ These observations provide some indirect evidence that lowering LDL cholesterol might be worthwhile among people with diabetes who do not already have symptomatic coronary disease. But, direct evidence that this is the case was not previously available, since the primary prevention trials of cholesterol-lowering statin therapy had involved only a few coronary events among a few hundred such people.^{24,25} The Heart Protection Study (HPS) prospectively aimed to assess the effects on vascular mortality and morbidity of a substantial LDL cholesterol reduction maintained for several years in a large cohort of diabetic individuals.

Patients and methods

Details of the study have been reported previously^{23,26,27} (see also www.hpsinfo.org) and are summarised below.

Recruitment and follow-up

Men and women aged about 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) were eligible provided they had a medical history of: diabetes mellitus; coronary disease; occlusive disease of non-coronary arteries; or treated hypertension (if also male and aged at least 65 years). Diabetes was classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS)^{23,28} broad definitions as either type 1 (diagnosis by age 30 years and insulin started within 1 year; or diagnosis by age 40 years, insulin started within 1 year, and less than 120% of desirable weight) or type 2 (all others with diagnosed diabetes). People were ineligible if their own doctor considered statin therapy to be clearly indicated or contraindicated, or if they had: myocardial infarction, stroke or hospital admission for angina within the previous 6 months; chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of substantially impaired renal function; inflammatory muscle disease or evidence of muscle problems; concurrent treatment with cyclosporin, fibrates, or high-dose niacin; child-bearing potential; severe heart failure; some life-threatening condition other than vascular disease or diabetes; or conditions that might limit long-term compliance.

Medical records were used to identify potentially eligible candidates who, with the agreement of their general practitioners, were invited to the local study clinics. At the initial screening visit, a non-fasting blood

sample was taken and guidance provided about modification of diet and other risk factors for vascular disease. Potentially eligible people were given detailed information about the study, asked for their written agreement to participate, and entered a prerandomisation run-in phase involving 4 weeks of placebo followed by 4–6 weeks of 40 mg simvastatin daily. The general practitioner was then informed of their patient's lipid profile (including LDL cholesterol measured directly), and asked to indicate whether they considered there to be a clear indication for, or contraindication to, statin therapy. Compliant individuals who did not have a major problem during the run-in were randomly allocated to receive 40 mg simvastatin daily or matching placebo calendar-packed tablets in a double-blind manner (and, separately, using a two-by-two factorial design, antioxidant vitamins or matching placebo capsules²⁹).

Participants were to be seen in the study clinics for routine follow-up checks at 4, 8, and 12 months, and then 6-monthly until the final follow-up visits. Those individuals who did not attend these clinic appointments were to be contacted by telephone at the time of their scheduled follow-up (or, alternatively, follow-up was to be maintained via their general practitioner). Compliance with study treatment was assessed at each follow-up by reviewing the calendar-packed tablets remaining. Participants and their general practitioners were advised of results emerging from other relevant studies^{17-20,24,25} and encouraged to use a non-study statin if they considered that it had become indicated. Blood samples were taken at each follow-up visit for central laboratory assay of alanine transaminase to monitor liver function, and of creatine kinase in any participant reporting unexplained muscle symptoms or concomitant use of a non-study statin with the study tablets. To assess the effects of the treatment allocation on the lipid profile during the study, assays were performed on non-fasting blood collected from a sample of participants due for follow-up at about the same time each year, and from all participants attending follow-up between August, 2000 and February, 2001 (ie, after an average of 4.6 years). Differences between the treatment groups in average blood lipid concentrations were based on comparisons between all those allocated simvastatin and all those allocated placebo, irrespective of whether or not they were still compliant (with any missing data imputed from the initial screening values, assuming no statin use). For participants recruited with diabetes, haemoglobin A_{1c} (HbA_{1c}) was measured in screening samples by an immunoturbidimetric method on a Beckman Synchron CX analyser (Beckman, Fullerton, CA, USA) with a reference range of 3.9–5.7%, and in follow-up samples by HPLC on a Menarini analyser (Menarini, Florence, Italy) with a reference range of 4.5–5.7% (and with standardisation against external assays).³⁰

Information was recorded at each follow-up about any suspected myocardial infarction, stroke, vascular procedure, cancer or other serious adverse experience, and about the main reasons for all other hospital admissions. Further details were sought from general practitioners (and, if considered necessary, hospital records) about all reports that might relate to major vascular events, cancers or deaths, and from UK national registries about the sites of cancers and the certified causes of deaths. All such information was reviewed and coded by coordinating centre clinical staff who were kept unaware of the participants' study treatment allocation and plasma lipid concentrations. Criteria required for classification of myocardial infarctions and strokes are

provided elsewhere.²⁷ Amputations were to be included within the non-coronary revascularisation outcome since, in this population, most were expected to be due to occlusive arterial disease. Analyses were based on confirmed plus unrefuted reports of events, with definite confirmation for 98% of the myocardial infarctions, strokes and revascularisations included.

Statistical analysis

The main comparisons involved logrank analyses of the first occurrence of particular events during the scheduled treatment period after randomisation among all those allocated 40 mg simvastatin daily versus all those allocated matching placebo tablets (ie, intention to treat).^{31,32} These logrank analyses yielded both the event rate ratio and the test of statistical significance (two-sided probability value). Assessments of the effects of treatment in different prespecified subcategories of prior disease (including diabetes) and of other presenting features were to be based on first major coronary events (defined as non-fatal myocardial infarction or death from coronary disease), and, particularly, on the even larger number of first major vascular events (defined as major coronary events, strokes of any type, and coronary or non-coronary revascularisations). It was estimated from previous studies in similar populations that randomisation of at least 2000 or 3000 individuals in any particular category should allow reliable assessment of a reduction of a quarter in the incidence rate of major vascular events and, somewhat less robustly, of major coronary events. Tests for heterogeneity or, if more appropriate, trend were to be used to determine whether the proportional effects observed in specific subcategories differed clearly from the overall effects (after due allowance for multiple comparisons). Subsidiary comparisons included assessment of the effects of allocation to simvastatin not just on the rate of first major vascular events following randomisation, but also on the numbers of first and subsequent events during the scheduled treatment period.

Role of the funding sources

The investigators were responsible for the study design, data collection, data analysis, data interpretation, and writing of the report, independently of all funding sources.

Results

Enrolment of patients

Between July, 1994 and May, 1997, 5963 people aged 40–80 years with diabetes mellitus were randomised in the HPS, along with a further 14 573 high-risk patients without diagnosed diabetes (table 1).²⁷ Among the participants known to have diabetes, previous myocardial infarction was reported at study entry by 1125 (19%), some other history of coronary disease by 856 (14%), other occlusive arterial disease alone by 1070 (18%), and no history of any arterial disease by 2912 (49%). According to predefined criteria,^{23,28} 615 (10%) were classified as having type 1 diabetes and 5348 (90%) as having type 2 diabetes, with mean intervals since diagnosis of 28.6 (SE 0.5) years and 9.3 (0.1) years, respectively. Insulin was being used at study entry by 95% of the participants with type 1 diabetes, whereas among those with type 2 diabetes, insulin was being used by 25%, sulphonylureas by 42%, metformin by 31%, and none of these agents by 21%. Compared to the participants without diabetes, those who had diabetes were younger, less likely to be male or to have occlusive arterial disease, and had higher blood pressure and body-mass index at baseline. The diabetic participants also presented with

slightly, but significantly, lower mean total and LDL cholesterol and higher mean triglyceride concentrations than those who did not have diabetes. The large size of the study (and the use of minimised randomisation³³) produced good balance between the treatment groups among participants for the main prognostic features that were measured (see subcategory figures below), and should have done likewise for those that were not.

Compliance and effects on blood lipids

The mean duration of follow-up was 4.8 years for all randomised participants known to have diabetes at entry to the study, and 5.0 years for all remaining participants. Compliance at each follow-up was defined as at least 80% of the scheduled simvastatin or placebo tablets having been taken since the previous follow-up. Among all participants allocated 40 mg simvastatin daily, average statin use during the scheduled treatment period was 85% (with 82% compliant with their allocated simvastatin, 3% on non-study statin alone, and 2% on both). By contrast, among all those allocated placebo, an average of 17% were taking non-study statin therapy during the study. Table 2 shows that this average absolute difference in statin use of 67% (85% minus 17%) between all participants allocated simvastatin and all those allocated placebo yielded an average difference in LDL cholesterol of 1.0 mmol/L (indicating that actual use of 40 mg simvastatin daily would reduce LDL cholesterol by an average of about 1.5 mmol/L in this population). Non-study statin use in the placebo group was more common among those who already had diagnosed coronary disease at entry, were younger, or had higher pretreatment total or LDL cholesterol concentrations, but was not much influenced by the presence of diabetes. In each subcategory in table 2 (including participants with diabetes), however, the average absolute difference in statin use was still about two-thirds (range 61–78%) and the average difference in LDL cholesterol was about 1.0 mmol/L (range 0.8–1.1). Table 3 shows that the average blood lipid differences achieved during the study between participants allocated simvastatin and those allocated placebo were similar among those with or without diagnosed diabetes at randomisation.

Baseline feature	Diabetes (n=5963)	No diabetes (n=14 573)
Age (years)	62.1 (8.9)	64.7 (8.1)
Men	4147 (70%)	11 307 (78%)
Smoking		
Never	1955 (33%)	3219 (22%)
Ex-cigarette	3250 (55%)	9199 (63%)
Current	758 (13%)	2155 (15%)
Vascular disease		
Prior MI	1125 (19%)	7385 (51%)
Other CHD	856 (14%)	4020 (28%)
Other vascular	1070 (18%)	2930 (20%)
No vascular	2912 (49%)	238 (2%)
Treated hypertension	2398 (40%)	6059 (42%)
Systolic BP (mm Hg)	148 (23)	143 (24)
Diastolic BP (mm Hg)	82 (12)	81 (12)
Body-mass index (kg/m ²)	28.6 (5.0)	27.2 (4.1)
Total cholesterol (mmol/L)	5.7 (1.03)	5.9 (1.00)
LDL cholesterol (mmol/L)	3.2 (0.82)	3.4 (0.82)
HDL cholesterol (mmol/L)	1.06 (0.36)	1.06 (0.31)
Triglycerides (mmol/L)	2.3 (1.59)	2.0 (1.27)
Apolipoprotein A ₁ (g/L)	1.20 (0.23)	1.20 (0.21)
Apolipoprotein B (g/L)	1.10 (0.24)	1.16 (0.23)

MI=myocardial infarction. CHD=coronary heart disease. BP=blood pressure. Values are mean (SD) or number of participants (%). Balance between the treatment groups within these, and other, categories is demonstrated in subcategory figures.

Table 1: Baseline characteristics of participants presenting with or without diabetes

Presenting feature	Use of study/non-study statin (%)			Plasma LDL cholesterol (mmol/L)		
	Simvastatin-allocated	Placebo-allocated	Absolute difference*	Simvastatin-allocated	Placebo-allocated	Absolute difference*
Prior disease						
CHD						
Diabetes	85%	24%	61%	2.2	3.0	-0.8
No diabetes	86%	20%	66%	2.3	3.3	-1.0
Other CVD						
Diabetes	82%	15%	67%	2.2	3.2	-1.0
No diabetes	82%	11%	72%	2.4	3.5	-1.0
No CVD†						
Diabetes	83%	11%	72%	2.2	3.1	-0.9
Age (years)						
<65						
Diabetes	85%	20%	64%	2.4	3.2	-0.9
No diabetes	86%	20%	66%	2.3	3.3	-0.9
≥65						
Diabetes	84%	13%	71%	2.2	3.3	-1.0
No diabetes	86%	15%	71%	2.3	3.3	-1.1
Total cholesterol (mmol/L)						
<5.0						
Diabetes	83%	5%	78%	1.8	2.6	-0.9
No diabetes	85%	13%	72%	2.1	3.0	-1.0
≥5.0						
Diabetes	86%	23%	62%	2.6	3.5	-1.0
No diabetes	86%	21%	65%	2.4	3.4	-1.0
LDL cholesterol (mmol/L)						
<3.0						
Diabetes	82%	6%	76%	1.8	2.6	-0.8
No diabetes	84%	9%	75%	1.9	2.8	-0.9
≥3.0						
Diabetes	84%	23%	62%	2.5	3.4	-0.9
No diabetes	86%	22%	64%	2.5	3.6	-1.0
All patients	85%	17%	67%	2.3	3.3	-1.0

CHD=coronary heart disease. CVD=cardiovascular disease. *Absolute difference in LDL cholesterol that would be produced by full compliance with 40 mg simvastatin daily can be estimated as the ratio of these two columns (eg, $-1.0/67\%=-1.4$ mmol/L for all patients). †Results not given for 237 patients included with treated hypertension alone.

Table 2: Average use of statin (study or non-study) and average plasma LDL cholesterol concentrations during follow-up

Effects on vascular events in the presence and absence of diabetes

Coronary events

Overall among all participants, allocation to simvastatin produced a highly significant 27% (95% CI 21–33, $p<0.0001$) proportional reduction in the incidence of first non-fatal myocardial infarction or coronary death following randomisation (figure 1). Among the diabetic participants there was a highly significant 27% (15–38, $p<0.0001$) reduction in these major coronary events, which was similar to the 27% (19–34, $p<0.0001$) reduction among the other high-risk individuals studied (heterogeneity $\chi^2=0.00$, $p=1.0$). For these diabetic participants, this represented a 20% (4–34) reduction in coronary mortality (193 [6.5%] simvastatin *vs* 239 [8.0%] placebo, $p=0.02$) and a 37% (20–50) reduction in first non-fatal myocardial infarction (105 [3.5%] *vs* 164 [5.5%], $p=0.0002$).

Lipids	Mean (SE) differences in concentrations*	
	Diabetes	No diabetes
Total cholesterol	-1.1 (0.04)	-1.2 (0.02)
LDL cholesterol	-0.9 (0.03)	-1.0 (0.02)
HDL cholesterol	0.01 (0.01)	0.04 (0.01)
Triglycerides	-0.3 (0.06)	-0.3 (0.03)
Apolipoprotein A ₁	-0.011 (0.019)	0.016 (0.007)
Apolipoprotein B	-0.263 (0.020)	-0.289 (0.010)

*Intention-to-treat comparisons (simvastatin minus placebo), with missing data imputed from initial pretreatment screening values; mmol/L for total, LDL, HDL, and triglycerides, and g/L for apolipoproteins.

Table 3: Average differences in plasma lipid concentrations during follow-up in participants with or without diabetes at study entry

Stroke

Overall, allocation to simvastatin produced a highly significant 25% (95% CI 15–34, $p<0.0001$) proportional reduction in the incidence of first non-fatal or fatal stroke following randomisation (figure 1). Among the diabetic participants there was a significant 24% (6–39, $p=0.01$) reduction in such strokes, which was similar to the 26% (14–36, $p=0.0002$) reduction among the other high-risk individuals studied (heterogeneity $\chi^2=0.02$, $p=0.9$). For these diabetic participants, this represented a 28% (8–44) reduction in strokes attributed to ischaemia (102 [3.4%] simvastatin *vs* 140 [4.7%] placebo, $p=0.01$), with no apparent difference in the small numbers of strokes attributed to haemorrhage (10 [0.3%] *vs* 15 [0.5%], $p=0.3$).

Revascularisation

Overall, allocation to simvastatin produced a highly significant 24% (95% CI 17–30, $p<0.0001$) proportional reduction in the incidence of first revascularisation procedure following randomisation (figure 1). Among the diabetic participants there was a significant 17% (3–30, $p=0.02$) reduction in such revascularisations, which was not significantly different from the 26% (18–33, $p<0.0001$) reduction among the other high-risk individuals studied (heterogeneity $\chi^2=1.17$, $p=0.3$). There was also a marginally significant reduction in the number of diabetic participants who developed peripheral macrovascular complications (156 [5.2%] simvastatin *vs* 194 [6.5%] placebo, $p=0.03$), which were defined prospectively as any peripheral artery surgery (38 [1.3%] *vs* 65 [2.2%]), peripheral angioplasty (57 [1.9%] *vs* 70 [2.3%]), leg amputation (67 [2.2%] *vs* 67 [2.2%]), or leg ulcer (40 [1.3%] *vs* 46 [1.5%]).

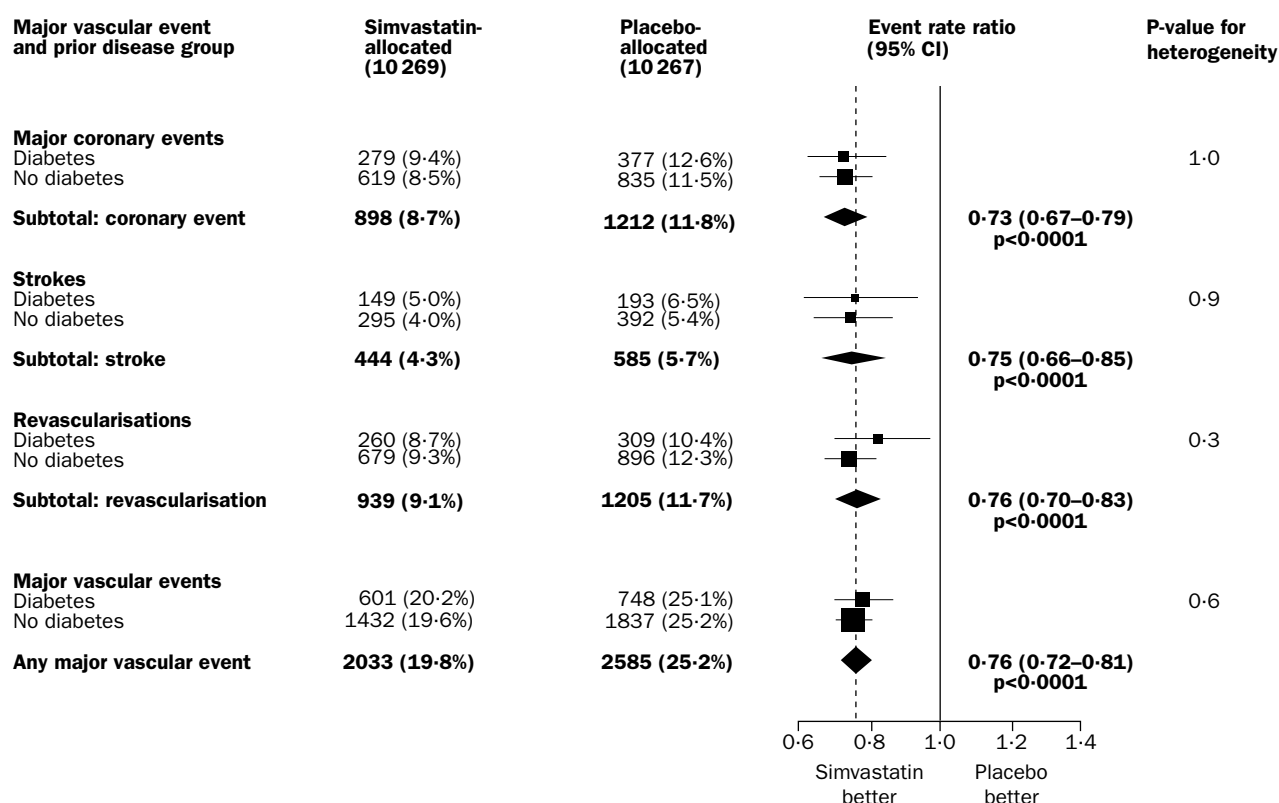


Figure 1: Effects of simvastatin allocation on first major coronary event, stroke, or revascularisation in participants presenting with or without diabetes

Analyses are of numbers of participants having a first event of each type during follow-up (with non-fatal and fatal events also considered separately in the text), so there is some overlap between different types of event. Rate ratios are plotted (black squares with area approximately proportional to number of events in each subdivision) comparing outcome among participants allocated simvastatin vs placebo, along with 95% CI (horizontal lines). For particular subtotals and totals, rate ratios are represented by diamonds. P-values for χ^2 tests of heterogeneity between rate ratios in different subcategories are given. Squares or diamonds to the left of the solid vertical line indicate benefit with simvastatin, which is conventionally significant ($p < 0.05$) within a particular subcategory considered on its own if the horizontal line or diamond does not overlap the solid vertical line. Broken vertical line indicates overall rate ratio for major vascular events.

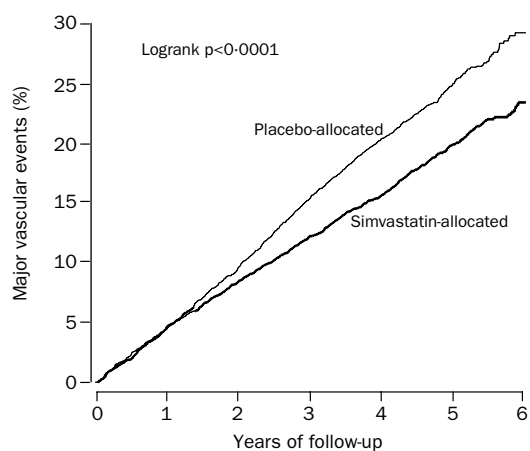
Major vascular events

When major coronary events, strokes, and revascularisations were considered together among all participants, allocation to simvastatin was associated with a very highly significant 24% (95% CI 19–28, $p < 0.0001$) proportional reduction in the first occurrence of any of these major vascular events (figure 1). Among the diabetic participants there was a highly significant 22% (13–30, $p < 0.0001$) reduction in the event rate, which was similar to the 25% (19–30, $p < 0.0001$) reduction among the other high-risk participants studied (heterogeneity $\chi^2 = 0.26$, $p = 0.6$). As a consequence, whereas about 25% of the placebo-allocated diabetic participants had a first major vascular event during 5 years of follow-up, only about 20% of those who were allocated simvastatin did so (figure 2; for major coronary events see <http://image.thelancet.com/extras/03art3418webfigure1.pdf>).

Effects on major vascular events in different circumstances among diabetic and other participants

The extreme statistical significance of the reduction in the rate of first major vascular events (z -score=9.3), and the large number of events on which it is based, allows reliable assessment of the effects of treatment in various different circumstances. Figures 3 and 4 indicate that the proportional reduction in risk among participants with or without diagnosed diabetes at study entry was about a quarter in each of the subcategories studied (for major coronary events see <http://image.thelancet.com/extras/03art3418webfigure2.pdf> and <http://image.thelancet.com/extras/03art3418webfigure3.pdf>).

In particular, among the 2912 diabetic patients who did not have any diagnosed coronary or other occlusive arterial disease at study entry, there was a highly significant 33% (95% CI 17–46, $p = 0.0003$) proportional reduction in first major vascular events (135 [9.3%] simvastatin vs 196 [13.5%] placebo, figure 3). The proportional risk reductions among all 5963 diabetic participants also appeared to be about a quarter irrespective of their sex or age, blood



Benefit (SE) per 1000 allocated simvastatin: -1 (6) 13 (8) 34 (9) 47 (10) 51 (15) 58 (48)

Figure 2: Life-table plot of effects of simvastatin allocation on percentages of diabetic participants having major vascular events

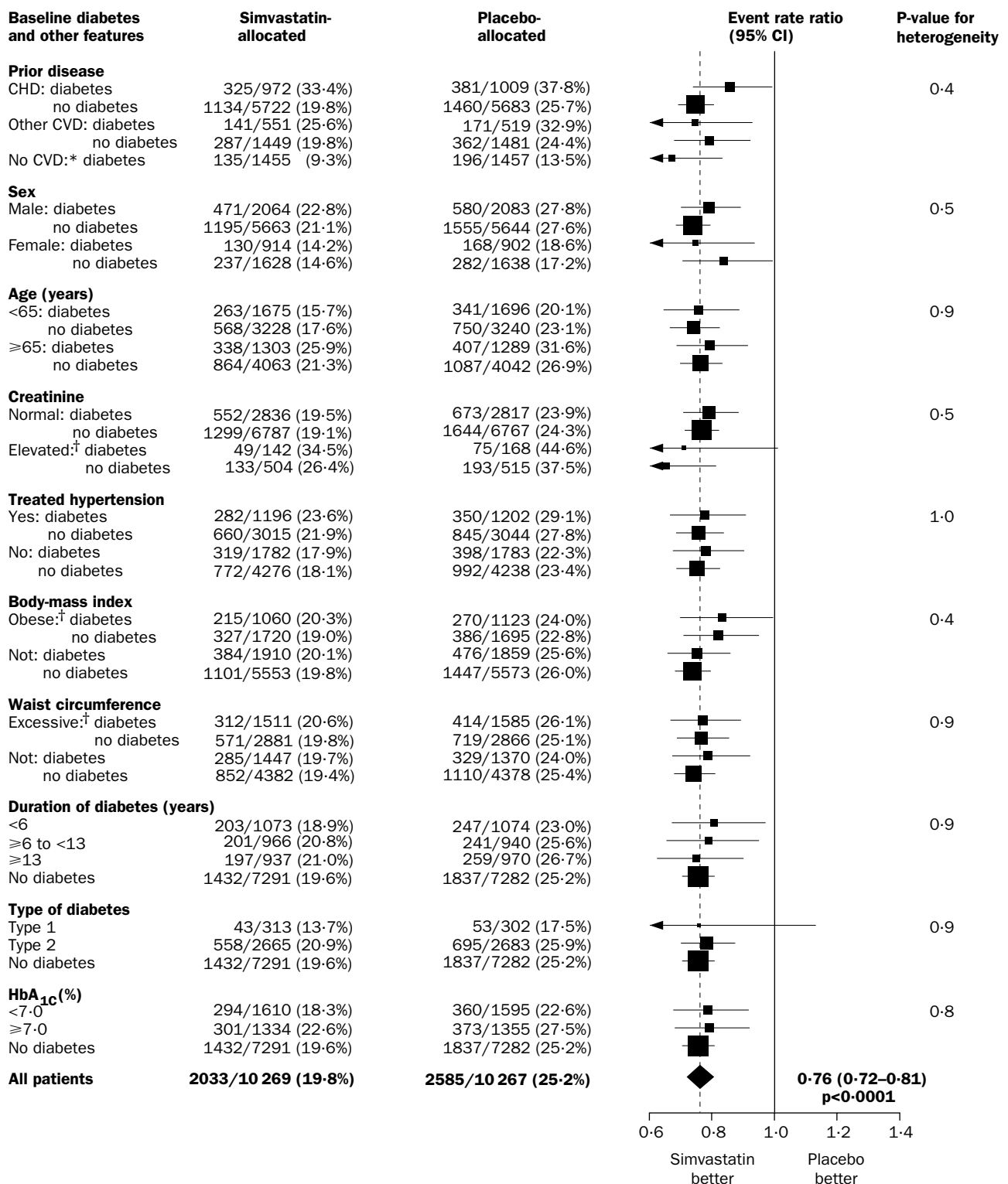


Figure 3: Effects of simvastatin allocation on first major vascular event in participants with or without diabetes subdivided by other presenting features

CHD=coronary heart disease. CVD=cardiovascular disease. Symbols and conventions as in figure 1. Treatment for hypertension recorded at entry to the study generally continued during follow-up. *Results not given for 237 participants with treated hypertension alone at study entry. †Elevated creatinine defined as ≥ 110 $\mu\text{mol/L}$ for women and ≥ 130 $\mu\text{mol/L}$ for men, but < 200 $\mu\text{mol/L}$ for both; obese defined as body-mass index ≥ 28 kg/m^2 for women and ≥ 30 kg/m^2 for men; excessive waist circumference defined as ≥ 88 cm for women and ≥ 102 cm for men.

creatinine concentration (although only a few hundred had concentrations of 150–200 $\mu\text{mol/L}$, with none above 200 $\mu\text{mol/L}$), treatment for hypertension, or body size or shape at study entry. Even when these analyses were restricted to the 2912 diabetic participants without known

occlusive arterial disease at randomisation, the proportional reduction in first major vascular events still appeared to be about the same among men (33% [SE 10] reduction, $p=0.002$) and women (30% [19] reduction, $p=0.1$), and among participants who were younger

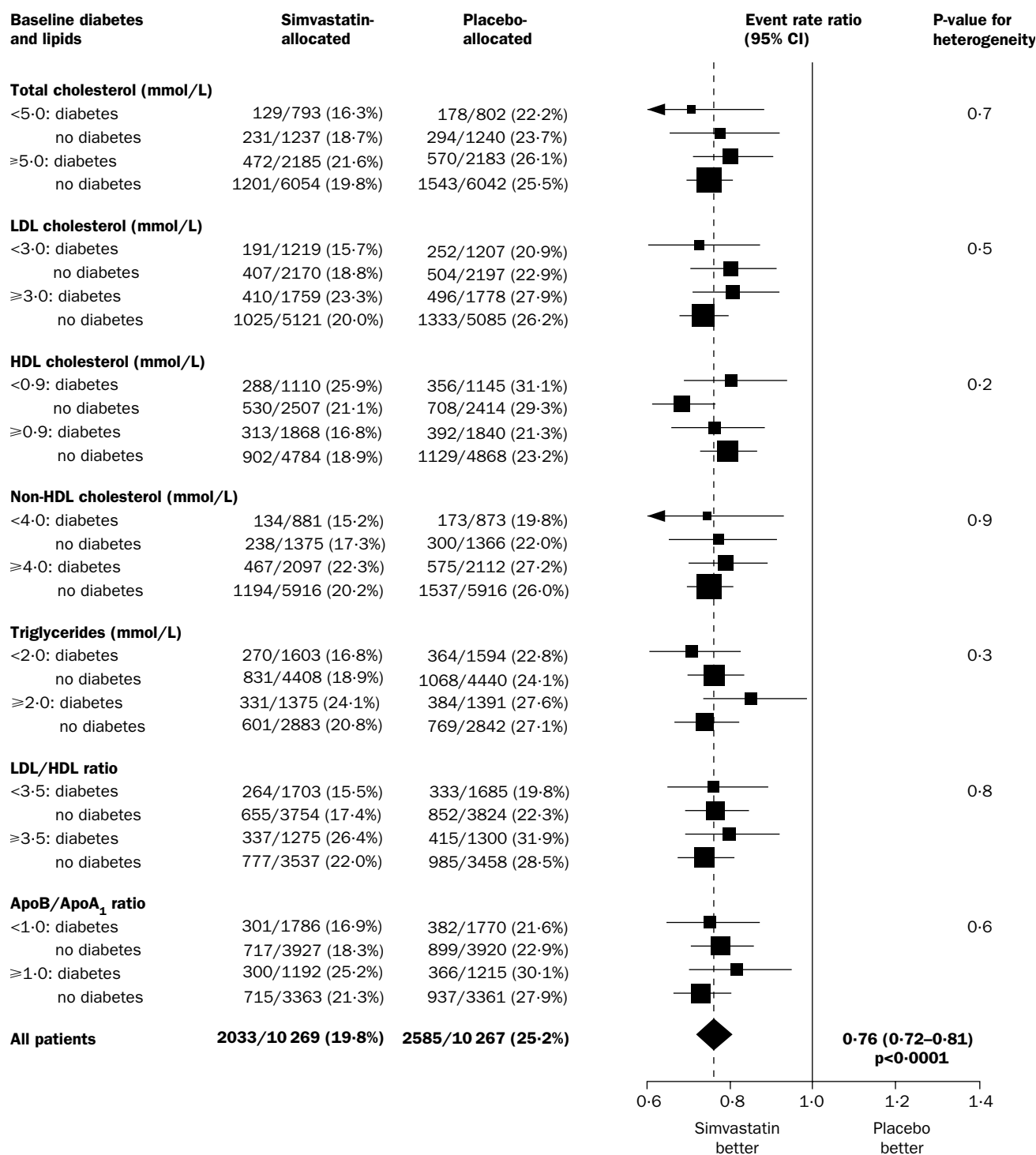


Figure 4: Effects of simvastatin allocation on first major vascular event in participants with or without diabetes subdivided by presenting blood lipid concentrations

ApoB=apolipoprotein B. ApoA₁=apolipoprotein A₁. Symbols and conventions as in figure 1. Lipid categories relate to measured values at the initial screening visit prior to starting any statin therapy.

(40–64 years: 33% [12] reduction, $p=0.006$) and older (65–80 years: 31% [14] reduction, $p=0.03$).

Similarly, the proportional reduction in risk appeared to be largely independent of the interval since diabetes diagnosis, the type of diabetes (although only 615 participants were classified as having type 1 diabetes), or the degree of glycaemic control when statin therapy was initiated (HbA_{1c} <7.0%: 21% [7] reduction, $p=0.002$; HbA_{1c} ≥7.0%: 21% [7] reduction, $p=0.002$). Most

notably, figure 4 shows that the proportional reduction in risk did not appear to be materially influenced by the pretreatment lipid concentrations (or various ratios of these measures). So, for example, there was a highly significant 27% (13–40, $p=0.0007$) reduction among the 2426 diabetic participants whose pretreatment measurements of LDL cholesterol were below 3.0 mmol/L (116 mg/dL), which was similar to the highly significant 20% (9–30, $p=0.0009$) reduction seen among

Prior disease group and event	Number of events		Events (SE) avoided per 1000 patients allocated simvastatin
	Simvastatin-allocated	Placebo-allocated	
Diabetes			
First events	601	748	49 (11)
All events	852	1109	85 (19)
No diabetes			
First events	1432	1837	56 (7)
All events	1911	2588	93 (11)
All patients			
First events	2033	2585	54 (6)
All events	2763	3697	91 (10)

Table 4: Effects of simvastatin allocation on first and all major vascular events in participants with or without diabetes

the other high-risk individuals recruited with LDL cholesterol below 3.0 mmol/L. Indeed, even among the 1343 diabetic participants without known occlusive arterial disease at randomisation whose pretreatment LDL cholesterol was below 3.0 mmol/L, there was a marginally significant 30% (1–50) reduction in first major vascular events (54 [8.0%] simvastatin *vs* 74 [11.1%] placebo, $p=0.05$).

Effects on first and subsequent major vascular events among diabetic patients

Overall in this high-risk population of diabetic and non-diabetic patients, 2585 (25.2%) placebo-allocated participants had a first major vascular event during mean follow-up of 5 years, and allocation to simvastatin reduced this rate by about a quarter (figure 1). But, these 2585 patients had 3697 first or subsequent major vascular events during this follow-up period, and the rate of these subsequent events was also reduced (table 4). Hence, whereas the 1.0 mmol/L reduction in LDL cholesterol observed on average during the study typically prevented 54 (SE 6) participants per 1000 from having at least one major vascular event, it prevented 91 (10) first or subsequent major vascular events per 1000 patients during this 5 year period of follow-up (table 4). Similarly, for the diabetic participants considered alone, allocation to simvastatin prevented 49 (11) per 1000 from having at least one major vascular event, but prevented 85 (19) first or subsequent major vascular events.

Effects on other outcomes in the presence and absence of diabetes

Renal function

Creatinine was measured in blood samples collected from all participants at the initial screening visit and, after an average of 4.6 years, from those attending follow-up between August, 2000 and February, 2001 (table 5). Plasma creatinine concentrations increased during follow-up as the population aged, but allocation to simvastatin was associated with a significantly smaller increase (7.13 [SE 0.24] $\mu\text{mol/L}$ simvastatin *vs* 8.94 [0.32] $\mu\text{mol/L}$ placebo, difference -1.81 [0.40] $\mu\text{mol/L}$; $p<0.0001$). The mean plasma creatinine concentration at entry to the study was slightly lower among participants with diagnosed diabetes than among the other high-risk participants, but the difference between the treatment groups in the plasma creatinine increase during follow-up was non-significantly larger (-2.18 [0.87] $\mu\text{mol/L}$ in diabetic participants *vs* -1.69 [0.44] $\mu\text{mol/L}$ in other high-risk participants; heterogeneity $p=0.6$). In order to investigate these differences further, estimates of glomerular filtration rate were derived retrospectively from the simplified Modification of Diet

in Renal Disease (MDRD) study formula.^{34,35} Overall, allocation to simvastatin was associated with a significantly smaller fall in the estimated glomerular filtration rate during follow-up (5.9 [0.1] mL/min simvastatin *vs* 6.7 [0.1] mL/min placebo, difference -0.8 [0.2] mL/min; $p=0.0003$). This difference, though small, appeared to be slightly larger among those who had diabetes than among those who did not (-1.4 [0.4] mL/min *vs* -0.5 [0.2] mL/min; heterogeneity $p=0.08$).

Diabetes control

Among a random sample of 1087 participants known to have diabetes at entry to the study, plasma HbA_{1c} concentration was measured in blood collected both at the initial screening visit (6.99% [SE 0.11] simvastatin *vs* 7.06% [0.10] placebo) and after an average of 4.6 years' follow-up (7.14% [0.06] *vs* 7.17% [0.06]). There was no significant difference between the treatment groups in the increase in HbA_{1c} concentration observed during follow-up (0.15% [0.09] *vs* 0.12% [0.09], difference 0.03% [0.13]; $p=0.8$), which suggests that simvastatin therapy does not materially affect diabetes control. Nor, among all 5963 participants known to have diabetes at randomisation, were there any apparent differences in reports of other diabetes-related outcomes (which was not a prespecified outcome), such as hospital admissions for unstable diabetes (91 [3.1%] *vs* 97 [3.2%]) or laser treatment for retinopathy (41 [1.4%] *vs* 36 [1.2%]).

Development of diabetes

Based on retrospective analysis of a previous trial,³⁶ it had been suggested that statin therapy might prevent the development of new diabetes. In the present study, this outcome was predefined as initiation of oral hypoglycaemic or insulin treatment, or a specific report of new diabetes, in participants who had not had diabetes diagnosed prior to randomisation. Among the 14 573 such participants, there was no significant difference between the treatment groups in the numbers who were found to have developed diabetes during follow-up (335 [4.6%] simvastatin *vs* 293 [4.0%] placebo, $p=0.10$).

Liver and muscle enzymes

Blood concentrations of alanine transaminase were measured at each follow-up, but elevations above four times the upper limit of normal were rare both among participants who had diabetes at entry to the study (14 [0.47%] simvastatin *vs* 11 [0.37%] placebo) and among

Prior disease group	Mean (SE) creatinine ($\mu\text{mol/L}$)	
	Simvastatin-allocated	Placebo-allocated
Diabetes		
Number of patients	2291	2172
Baseline	87.74 (0.39)	87.27 (0.39)
Follow-up	98.44 (0.68)	100.15 (0.81)
Difference in change	-2.18 (0.87), $p<0.05$	
No diabetes		
Number of patients	5708	5525
Baseline	94.91 (0.26)	95.11 (0.25)
Follow-up	100.61 (0.34)	102.50 (0.44)
Difference in change	-1.69 (0.44), $p<0.001$	
All patients		
Number of patients	7999	7697
Baseline	92.86 (0.22)	92.90 (0.22)
Follow-up	99.99 (0.31)	101.84 (0.39)
Difference in change	-1.81 (0.40); $p<0.0001$	

Mean follow-up of 4.6 years among all participants with creatinine measurements at baseline and follow-up.

Table 5: Effects of simvastatin allocation on plasma creatinine concentrations in participants with or without diabetes

those who did not (29 [0.40%] *vs* 21 [0.29%]). Creatine kinase was measured in any participant reporting unexplained muscle symptoms or concomitant use of a non-study statin, but few were found to have creatine kinase elevations above ten times the upper limit of normal (diabetic participants: 4 [0.13%] simvastatin *vs* 2 [0.07%] placebo; other participants: 7 [0.10%] *vs* 4 [0.05%]).

Discussion

Benefits for diabetic patients irrespective of existing arterial disease or presenting lipid concentrations

The HPS provides definitive evidence that cholesterol-lowering statin therapy can produce substantial reductions in the risk of heart attacks, of strokes, and of revascularisations in people with diabetes, even if they do not already have diagnosed coronary or other occlusive arterial disease. The study involved about 6000 patients with known diabetes, of whom 2000 had pre-existing coronary disease, another 1000 had other occlusive arterial disease, and the remaining 3000 had no evidence of either coronary or other occlusive arterial disease. An average difference in LDL cholesterol of 1.0 mmol/L (39 mg/dL) during the trial significantly reduced the risk of major vascular events by about a quarter in these diabetic individuals—which was similar to the proportional reduction seen among the non-diabetic participants—irrespective of any pre-existing occlusive arterial disease or their presenting age, sex, lipid concentrations, or glycaemic control.

Previously, only about 1500 diabetic patients with symptomatic coronary disease^{20–23} and 200 without coronary disease^{24,25} had been included in randomised outcome trials of statin therapy. Analysis of those studies suggested that cholesterol-lowering therapy might produce worthwhile benefits in diabetic patients, but these observations required prospective confirmation in large randomised trials. In addition to HPS, results have been reported recently from two other randomised trials of statin therapy that involved substantial numbers of patients with diabetes. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),³⁷ 40 mg pravastatin daily was compared with usual care (ie, no placebo control) among 10 355 hypertensive patients. Type 2 diabetes was recorded at entry in 3638 of the participants, with some of those diabetic patients additionally having known coronary or other occlusive arterial disease. Chiefly due to widespread use of non-study statin therapy in the usual care group of that trial, however, the average difference in LDL cholesterol concentrations measured between these two treatment groups was only about 0.6 mmol/L during 4.8 years of follow-up. Most probably as a consequence, only a small and non-significant 9% reduction (95% CI 4% increase to 21% decrease) in the coronary event rate was observed among the pravastatin-allocated participants, albeit with similar proportional reductions in the presence or absence of diabetes. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),³⁸ 10 mg atorvastatin daily was compared with placebo among 10 305 hypertensive patients, of whom 2532 had type 2 diabetes at entry (again with some additionally having occlusive arterial disease). Overall, the average difference in LDL cholesterol concentrations between these two treatment groups was about 1.1 mmol/L during 3.3 years of follow-up, and allocation to atorvastatin was associated with a highly significant 36% (95% CI 17–50, $p=0.0005$) reduction in major coronary events. There was no significant difference between the proportional reductions in coronary risk observed among the diabetic and non-diabetic participants in that trial, but

there were too few coronary events among the patients with diabetes (38 [3.0%] atorvastatin *vs* 46 [3.6%] placebo, $p=0.4$) to assess the effects reliably within that subgroup considered on its own.

Current guidelines for diabetes emphasise the importance of good glycaemic control for all diabetic patients, but do not generally recommend initiating statin therapy unless blood cholesterol concentrations are considered to be elevated (eg, LDL higher than about 3.0–3.4 mmol/L [116–130 mg/dL]).^{9,10,39–41} HPS now shows that lowering LDL cholesterol from below 3.0 mmol/L to below 2.0 mmol/L (ie, <116 to <77 mg/dL) in people with diabetes reduces macrovascular disease risk by about a quarter, which is similar to the proportional reduction in risk produced by a 1.0 mmol/L reduction at higher concentrations. Moreover, among the types of diabetic patients studied in HPS, the absolute benefits produced by a 1.0 mmol/L reduction in LDL were similar, and substantial, both among those with pretreatment LDL below 3.0 mmol/L and among those with higher levels. As people with diabetes typically have blood concentrations of total and LDL cholesterol that are similar to those in the general population,^{3,6} these findings are relevant for a large number of high-risk individuals who are not currently being offered cholesterol-lowering therapy.

Absolute benefit depends chiefly on absolute risk of heart attacks and strokes

Compared to participants with diabetes, the non-diabetic population in HPS was generally older and more likely to have been included because of prior myocardial infarction (51% of non-diabetic *vs* 19% of diabetic participants) or other occlusive arterial disease (48% *vs* 32%). These differences are likely to explain the similar absolute risks of vascular events in participants with or without diabetes (see figure 1), since the chief determinant of absolute risk was the type of pre-existing

Risk reductions (SE):

Proportional	32.9% (9.1)	24.5% (3.1)	18.4% (5.7)
Absolute/1000	44 (12)	62 (8)	66 (21)
P-value	0.0003	<0.0001	0.002

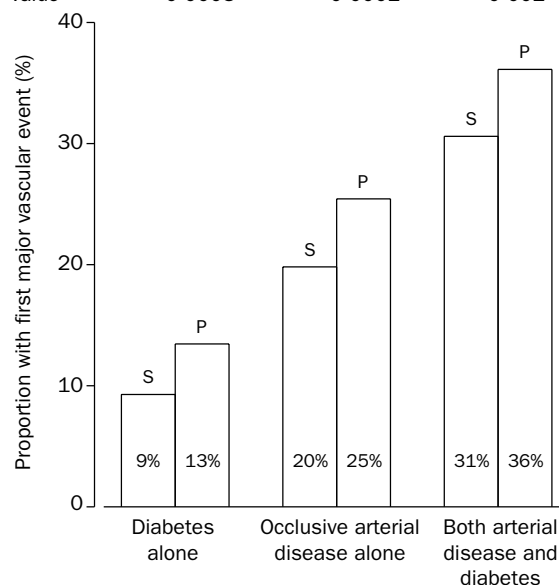


Figure 5: Absolute effects of simvastatin allocation on 5-year rates of first major vascular event among participants with diabetes, occlusive arterial disease, or both

S=simvastatin-allocated. P=placebo-allocated.

disease (ie, coronary disease, other occlusive arterial disease, diabetes, or some combination of these conditions) rather than the initial concentrations of blood lipids or other characteristics. For example, among people in the placebo group, the 5-year rates of a first major vascular event following entry to the study ranged from 13% for those with diabetes but no occlusive arterial disease to 36% for those with both diabetes and vascular disease, with an intermediate rate of 25% in those with occlusive arterial disease alone (figure 5). By contrast, among the diabetic patients without occlusive arterial disease who were studied, the absolute risks of major vascular events were influenced to a lesser extent by their initial concentrations of blood lipids (placebo group 5-year rate with LDL <3.0 mmol/L: 11%; and ≥ 3.0 mmol/L: 15%), their sex (male: 16%; female: 9%), or their presenting age (40–49 years: 7%; 50–59 years: 11%; 60–69 years: 17%; 70–80 years: 18%). Hence, the overall reduction in risk of about a quarter produced by a 1.0 mmol/L reduction in LDL cholesterol would typically be expected to translate into avoidance of major vascular events during 5 years in about 30 per 1000 diabetic individuals without occlusive arterial disease compared to about 90 per 1000 people who had both diabetes and arterial disease. (The somewhat larger difference in figure 5 among participants with diabetes alone may reflect the play of chance on the proportional reduction in risk observed within just that relatively small subgroup, by contrast with estimates of the absolute benefit derived from the more reliably determined reduction of a quarter observed overall.)

Continued treatment reduces rates of first and subsequent vascular events

During HPS, an average of about a sixth of the participants allocated 40 mg simvastatin daily stopped taking statin therapy, and about a sixth of those allocated placebo started to take a statin. As a consequence, the average difference in LDL cholesterol of about 1.0 mmol/L (39 mg/dL) that was observed between all those allocated simvastatin and all those allocated placebo represents only about two-thirds of the LDL cholesterol difference produced by actual use of 40 mg simvastatin daily. Similarly, the reduction of about a quarter in major vascular events in the intention-to-treat comparisons is likely to represent only about two-thirds of the risk reduction produced by actual compliance with this statin regimen. Hence, actual use of 40 mg simvastatin daily would lower LDL cholesterol by about 1.5 mmol/L (58 mg/dL) in this population, and would probably reduce the rates of heart attacks, strokes, and revascularisations by about a third. Consequently, among the types of diabetic patient typically included in HPS (with 5-year placebo-group event rates of about 25%), treatment for 5 years would be expected to prevent about 80 per 1000 from having at least one of these major vascular events. Similarly, among the diabetic participants without occlusive arterial disease, 5 years of this statin regimen should prevent such events in about 45 people per 1000 treated.

Previous statin trials have tended to concentrate on the effects of the allocated treatment on the incidence of the first vascular event of each particular type that occurs after randomisation. The present analyses of HPS show, however, that continued treatment reduces the rate not just of the first occurrence of such events but also of subsequent events. Indeed, the absolute reductions in the number of major vascular events avoided per 1000 people are more than 50% greater than the

number of people per 1000 who avoided such events, both among participants known to have diabetes at entry to the study and among those who did not. Hence, among the 80 diabetic participants per 1000 who would typically be expected to avoid at least one major vascular event during 5 years of treatment, more than 120 first or subsequent major vascular events would be avoided. Similarly, among the diabetic participants without occlusive arterial disease, about 70 first or subsequent events should be prevented among the 45 people per 1000 treated who avoid at least one event.

Effects on other diabetes-related outcomes

There did not appear to be any effect of 5 years of simvastatin treatment on glycaemic control or other diabetic complications among participants in HPS who had diagnosed diabetes at entry to the study. Nor was there any evidence to support the previous suggestion, based on a retrospective analysis of 139 participants who became diabetic during a previous trial with pravastatin,³⁶ that statin therapy might prevent the development of new diabetes. In HPS, a marginally significant reduction was observed in the number of diabetic participants allocated simvastatin who developed peripheral macrovascular complications, which chiefly reflected a significant reduction in peripheral artery surgery or angioplasty (with little apparent effect on amputations or leg ulceration). Allocation to simvastatin was also associated with a significantly smaller increase in mean plasma creatinine concentration during the follow-up period, and a retrospective analysis suggests that this difference may reflect a beneficial effect on renal function which was more marked among the diabetic participants. As people with blood creatinine concentrations above 200 $\mu\text{mol/L}$ were excluded from the present study, further large trials are required to determine prospectively whether statin therapy can prevent clinically relevant changes in renal function among people at particular risk of developing end-stage kidney disease.

Conclusions for avoidance of macrovascular complications in people with diabetes

The finding in HPS that cholesterol-lowering with 40 mg simvastatin daily produces substantial reductions in the risks of heart attacks and strokes among people with diabetes, and in UKPDS and the Heart Outcomes Prevention Evaluation (HOPE)^{42,43} that blood pressure lowering therapy can do likewise (by contrast with the lack of good evidence for such effects with stricter glycaemic control⁴⁴), has important implications for avoidance of the macrovascular complications of diabetes. In particular, these results support a renewed emphasis on the control of macrovascular risk factors other than hyperglycaemia (eg, reducing cholesterol and blood pressure, and stopping smoking^{42,43,45,46}) in people with diabetes. HPS has shown that the benefits of cholesterol-lowering statin therapy are additional to those of other cardioprotective treatments (such as angiotensin-converting-enzyme inhibitors, aspirin, and β blockers),²⁷ and are not materially influenced by the degree of glycaemic control in diabetic patients. It also shows that 40 mg simvastatin daily is safe and well tolerated.²⁷ Based on these results, decisions about whether to initiate statin therapy should now be guided by an individual's estimated risk of having either a heart attack or a stroke, or needing some major revascularisation procedure (rather than, as at present,^{39–41} just their risk of a coronary event, which typically underestimates the likely benefits by about half). In

particular, statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of such major vascular events, irrespective of their initial cholesterol concentrations.

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Conflict of interest statement

The Clinical Trial Service Unit has a staff policy of not accepting honoraria or other payments directly or indirectly from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. Coordinating centre members of the writing committee (R Collins, J Armitage, S Parish, R Peto) have, therefore, only had such costs reimbursed. P Sleight has received honoraria as well as such reimbursement of costs.

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