

Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions

Heart Protection Study Collaborative Group*

Summary

Background Lower blood cholesterol concentrations have consistently been found to be strongly associated with lower risks of coronary disease but not with lower risks of stroke. Despite this observation, previous randomised trials had indicated that cholesterol-lowering statin therapy reduces the risk of stroke, but large-scale prospective confirmation has been needed.

Methods 3280 adults with cerebrovascular disease, and an additional 17 256 with other occlusive arterial disease or diabetes, were randomly allocated 40 mg simvastatin daily or matching placebo. Subgroup analyses were prespecified of first "major vascular event" (ie, non-fatal myocardial infarction or coronary death, stroke of any type, or any revascularisation procedure) in prior disease subcategories. Subsidiary outcomes included any stroke, and stroke subtype. 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 Overall, there was a highly significant 25% (95% CI 15–34) proportional reduction in the first event rate for stroke (444 [4.3%] simvastatin vs 585 [5.7%] placebo; $p < 0.0001$), reflecting a definite 28% (19–37) reduction in presumed ischaemic strokes ($p < 0.0001$) and no apparent difference in strokes attributed to haemorrhage (51 [0.5%] vs 53 [0.5%]; rate ratio 0.95 [0.65–1.40]; $p = 0.8$). In addition, simvastatin reduced the numbers having transient cerebral ischaemic attacks alone (2.0% vs 2.4%; $p = 0.02$) or requiring carotid endarterectomy or angioplasty (0.4% vs 0.8%; $p = 0.0003$). The reduction in stroke was not significant during the first year, but was already significant ($p = 0.0004$) by the end of the second year. Among patients with pre-existing cerebrovascular disease there was no apparent reduction in the stroke rate, but there was a highly significant 20% (8–29) reduction in the rate of any major vascular event (406 [24.7%] vs 488 [29.8%]; $p = 0.001$). The proportional reductions in stroke were about one-quarter in each of the other subcategories of participant studied, including: those with coronary disease or diabetes; those aged under or over 70 years at entry; and those presenting with different levels of blood pressure or lipids (even when the pretreatment LDL cholesterol was below 3.0 mmol/L [116 mg/dL]).

Interpretation Much larger numbers of people in the present study suffered a stroke than in any previous cholesterol-lowering trial. The results demonstrate that statin therapy rapidly reduces the incidence not only of coronary events but also of ischaemic strokes, with no apparent effect on cerebral haemorrhage, even among individuals who do not have high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of ischaemic strokes by about one-quarter and so, after making allowance for non-compliance in the trial, actual use of this regimen would probably reduce the stroke rate by about a third. HPS also provides definitive evidence that statin therapy is beneficial for people with pre-existing cerebrovascular disease, even if they do not already have manifest coronary disease.

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Introduction

Observational studies in different populations indicate a strong continuous positive relation between coronary heart disease risk and blood cholesterol concentration that extends well below the range commonly seen in Western populations.^{1–5} Little association has been found in observational studies between blood total cholesterol concentrations and the risk of any type of stroke, but there does appear to be a positive association with ischaemic stroke risk (particularly at younger ages).^{6–11} It has been suggested, however, that this might be counterbalanced by a weak negative association with haemorrhagic stroke risk (perhaps especially among people with higher blood pressure).^{8–11}

In the randomised trials of cholesterol-lowering drugs or diets that were conducted before the introduction of the statins, blood cholesterol concentrations were typically reduced by only about 0.5 mmol/L (19 mg/dL) and coronary events reduced by only about 10–15%.¹¹ The stroke risk did not appear to be altered in a meta-analysis of those trials (relative risk 1.0), but the 95% CI (0.8–1.6) includes the possibility of a 10–15% reduction in stroke.¹² More recently, in previous trials of statin therapy, LDL cholesterol concentrations were typically reduced by about 1.0 mmol/L (39 mg/dL) and coronary events reduced by about 20–25%.¹¹ Although there were too few strokes during each of those trials^{13–18} to allow reliable assessment of the effects on stroke risk, meta-analyses did indicate that statin therapy reduces the risk not just of coronary events but also of strokes.^{11,19,20} This observation was supported by the finding that cholesterol-lowering with statin therapy slowed the progression of carotid atherosclerosis.^{21–23} More definitive evidence was required, however, about the magnitude of any effects of cholesterol-lowering on stroke subtypes and about the effects on stroke in different circumstances.^{24,25} The large randomised Heart Protection Study (HPS) prospectively aimed to assess reliably the effects on stroke incidence of a substantial LDL cholesterol

*Collaborators and participating hospitals are listed at <http://image.thelancet.com/extras/04art2126webappendix.pdf>

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reduction maintained for several years in a wide range of individuals at substantial risk of vascular disease.

Methods

Details of the study have been reported previously^{26–28} (see also <http://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: cerebrovascular disease (ie, non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemic attack, or carotid endarterectomy or angioplasty); coronary disease; other occlusive arterial disease; diabetes mellitus; or treated hypertension (if also male and aged at least 65 years). People were ineligible if their own doctor considered statin therapy to be clearly indicated or contraindicated, or if they had: stroke, myocardial infarction, 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 ciclosporin, fibrates, or high-dose niacin; child-bearing potential; severe heart failure; life-threatening condition other than vascular disease or diabetes; or conditions that might limit long-term compliance.

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 pre-randomisation “run-in” phase involving 4 weeks of placebo followed by 4–6 weeks of 40 mg simvastatin daily. Compliant and eligible individuals who were not considered by their own doctors to have a clear indication for, or contraindication to, statin therapy were then randomly allocated to receive 40 mg simvastatin daily or matching placebo calendar-packed tablets for about 5 years (and separately, using a 2×2 factorial design, to receive antioxidant vitamins or matching placebo capsules²⁶). Participants were to be seen in the study clinics for routine follow-up checks at 4, 8, and 12 months, and then 6-monthly. 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 via their general practitioner). Participants and their general practitioners were advised of results emerging from other relevant studies, and encouraged to use a non-study statin if they considered that it had become clearly indicated. Blood samples were taken at each follow-up visit for central laboratory assay of alanine aminotransferase to monitor liver function, and of creatine kinase in any participant reporting unexplained muscle symptoms or concomitant use of a non-study statin. To assess the effects of the treatment allocation on the lipid profile, 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 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.

Information was recorded at each follow-up about any suspected stroke, myocardial infarction, 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 strokes, other major vascular events, cancers or deaths, and from UK national registries about any cancers and the certified causes of any deaths. All such information was reviewed and coded by coordinating centre clinical staff who were unaware of the participants' study treatment allocation and plasma lipid concentrations. Stroke confirmation required evidence indicating the rapid onset of a focal or global (eg, coma) neurological deficit lasting more than 24 h or leading to death.²⁹ Neurological imaging or necropsy reports were required to classify confirmed strokes as ischaemic or haemorrhagic, with other strokes classified as being of unknown aetiology. (Subarachnoid haemorrhage was to be included as stroke, but subdural haematoma or transient cerebral ischaemia was not.) The severity of the stroke was classified as “mild” when there seemed to be little or no interference with lifestyle (ie, equivalent to a modified Rankin score of 0, 1, or 2), “moderate” when some help was needed for everyday activities (ie, Rankin 3 or 4), or “severe” when constant care and attention was needed (ie, Rankin 5).³⁰ The stroke was classified as “fatal” when it was considered to have led to death within about 1 month, either directly or through some non-neurological complication (eg, pneumonia). Transient cerebral ischaemic attacks did not include reports of amaurosis fugax. Criteria required for classification of myocardial infarction are provided elsewhere.²⁷ Analyses were based on confirmed plus unrefuted reports of events, with definite confirmation for 98% of the strokes, myocardial infarctions, and revascularisations that are included in the present report.

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 These logrank analyses yielded both the event rate ratio and the test of statistical significance (two-sided probability value). The prespecified secondary outcomes included total (non-fatal or fatal) stroke and, separately, presumed ischaemic stroke (ie, all strokes not confirmed to be haemorrhagic), and the tertiary outcomes included cerebral haemorrhage. Assessments of the effects of allocated treatment in different subcategories of prior disease and of other presenting features were to be based particularly on first “major vascular events” (defined as non-fatal myocardial infarction or coronary death, stroke of any type, and coronary or non-coronary revascularisation). 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 about a quarter in the incidence rate of major vascular events (but not of stroke considered on its own).^{26,27} Tests for heterogeneity or, where 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).

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.

Baseline feature	Cerebrovascular disease (n=3280)	No cerebrovascular disease (n=17 256)
Age (years)	65.5 (7.8)	63.7 (8.5)
Men	2445 (75%)	13 009 (75%)
Smoking		
Never regular	806 (25%)	4368 (25%)
Ex-cigarette	1940 (59%)	10 509 (61%)
Current	534 (16%)	2379 (14%)
Coronary disease		
Prior MI	896 (27%)	7614 (44%)
Other CHD	564 (17%)	4312 (25%)
None	1820 (55%)	5330 (31%)
Treated hypertension	1655 (50%)	6802 (39%)
Systolic BP (mm Hg)	147 (24)	144 (23)
Diastolic BP (mm Hg)	83 (12)	81 (12)
Body-mass index (kg/m ²)	27.3 (4.3)	27.7 (4.5)
Plasma lipids		
Total cholesterol (mmol/L)	5.9 (1.06)	5.8 (1.01)
LDL cholesterol (mmol/L)	3.4 (0.84)	3.4 (0.82)
HDL cholesterol (mmol/L)	1.08 (0.34)	1.05 (0.33)
Triglycerides (mmol/L)	2.1 (1.34)	2.1 (1.38)
Apolipoprotein A ₁ (mg/dL)	1.21 (0.22)	1.20 (0.22)
Apolipoprotein B (mg/dL)	1.16 (0.24)	1.14 (0.23)

MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure. Values are mean (SD) or number of participants (%).

Table 1: Baseline characteristics of participants presenting with or without cerebrovascular disease

Results

Patient enrolment

Between July, 1994, and May, 1997, 3280 people aged 40–80 years with a history of cerebrovascular disease were randomised, along with a further 17 256 high-risk patients who did not have diagnosed cerebrovascular disease (table 1).²⁷ Among the participants known to have cerebrovascular disease, previous ischaemic strokes were reported at study entry by 2070 (63%), transient cerebral ischaemic attacks by 1504 (46%), and carotid endarterectomy or angioplasty by 343 (10%), with overlap between these categories (ie, only 60 [2%] had not had a stroke or transient cerebral ischaemic attack). The mean interval since the most recent stroke or transient

ischaemic attack was 4.3 (SE 0.1) years. Aspirin was being used at study entry by 77% of the participants with cerebrovascular disease, while among the remaining participants it was being used by 77% of those who had coronary disease and by 23% of those who did not; oral anticoagulants were being used by 11%, 4%, and 3% of these respective groups. Participants who had pre-existing cerebrovascular disease were, on average, older than those who did not, with more treated hypertension and higher blood pressures, but—since the remaining participants had to have some other form of vascular disease or diabetes—were less likely to have had myocardial infarction or other coronary disease (table 1). Pretreatment plasma lipid concentrations were similar among participants with or without diagnosed cerebrovascular disease. The large size of the study, and the use of minimised randomisation,³² produced good balance between the treatment groups for the disease categories and other main prognostic features that were recorded (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 cerebrovascular disease at entry to the study and 5.0 years for all other 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 the 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 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 those 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

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						
Cerebrovascular	84%	21%	64%	2.4	3.3	-0.9
No cerebrovascular	86%	21%	66%	2.3	3.2	-1.0
No CHD						
Cerebrovascular	83%	12%	71%	2.4	3.4	-1.0
No cerebrovascular	82%	11%	71%	2.3	3.2	-1.0
Age (years)						
<65	85%	20%	64%	2.4	3.2	-0.9
≥65 to <70	87%	18%	69%	2.2	3.3	-1.0
≥70	84%	12%	72%	2.2	3.3	-1.1
Treated hypertension						
Yes	85%	19%	66%	2.3	3.2	-0.9
No	85%	17%	68%	2.3	3.3	-1.0
Total cholesterol (mmol/L)						
<5.0	83%	5%	78%	1.8	2.6	-0.9
≥5.0 to <6.0	85%	15%	70%	2.1	3.1	-1.0
≥6.0	86%	26%	60%	2.7	3.7	-1.0
LDL cholesterol (mmol/L)						
<3.0	83%	8%	75%	1.8	2.7	-0.9
≥3.0 to <3.5	86%	16%	69%	2.2	3.2	-1.0
≥3.5	86%	26%	60%	2.7	3.7	-1.0
All patients	85%	17%	67%	2.3	3.3	-1.0

CHD=coronary heart disease; *The 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 (for example, $-1.0/67\%=-1.5$ mmol/L).

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

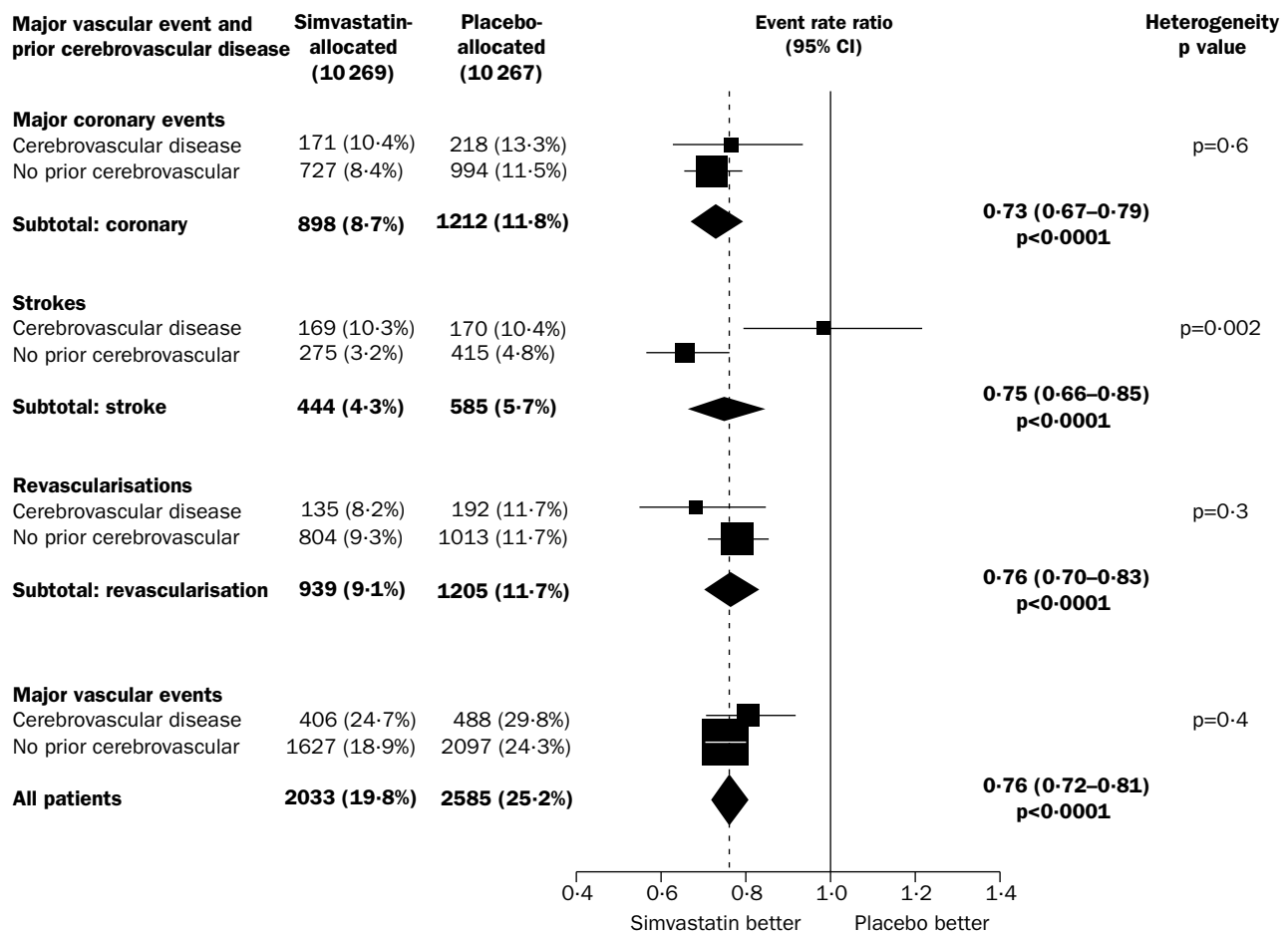


Figure 1: Effects of simvastatin allocation on first major coronary event, stroke, or revascularisation in participants subdivided by prior cerebrovascular disease

Analyses are of numbers of participants having a first event of each type during follow-up, so there is some overlap between different types of event. Rate ratios (RRs) are plotted (black squares with area approximately proportional to number of people having events in each subdivision) comparing outcome among participants allocated simvastatin versus placebo, along with 95% CIs (horizontal lines; ending with arrow head when CI extends beyond scale). For particular subtotals and totals, RR and 95% CI are represented by a diamond, with values given alongside. p values for χ^2 tests of heterogeneity between RRs 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 the overall RR.

simvastatin daily would reduce LDL cholesterol by an average of about 1.5 mmol/L [58 mg/dL] 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 materially influenced by pre-existing cerebrovascular disease. In each subcategory in table 2, however, the average absolute difference in statin use was still about two-thirds (range 60–78%) and the average difference in LDL cholesterol was about 1.0 mmol/L (range 0.9–1.1 mmol/L).

Effects on major vascular events subdivided by prior cerebrovascular disease

Overall, allocation to simvastatin produced a very highly significant 24% (95% CI 19–28; $p<0.0001$) proportional reduction in the first occurrence of non-fatal myocardial infarction or coronary death (ie, “major coronary event”), stroke of any type, or any revascularisation procedure following randomisation (figure 1). Among the participants with cerebrovascular disease at study entry there was a highly significant 20% (8–29; $p=0.001$) proportional reduction in the incidence rate of these major vascular events, which was similar to the 25%

(20–30; $p<0.0001$) reduction among the other high-risk participants studied (heterogeneity $p=0.4$). Indeed, even among the 1820 patients with cerebrovascular disease but no coronary disease at study entry, there was a significant 23% (6–37) reduction in major vascular events (172 [18.7%] simvastatin *vs* 212 [23.6%] placebo; $p=0.01$). The reduction in major vascular events among all participants with pre-existing cerebrovascular disease represented significant reductions of 23% (7–37; $p=0.008$) in the first major coronary event rate and of 32% (15–45; $p=0.0005$) in the first revascularisation rate, which were similar to the proportional reductions observed in these outcomes among the other high-risk individuals studied. The 24% (17–30; $p<0.0001$) reduction in the rate of revascularisation procedures observed overall among all participants reflected a 30% (22–38) reduction in coronary revascularisation (513 [5.0%] *vs* 725 [7.1%]; $p<0.0001$) and a 16% (5–26) reduction in non-coronary revascularisation (450 [4.4%] *vs* 532 [5.2%]; $p=0.006$). Half of that difference in non-coronary revascularisation involved a definite reduction in carotid endarterectomy or angioplasty (42 [0.4%] *vs* 82 [0.8%]; $p=0.0003$), with much of it observed among participants with pre-existing cerebrovascular disease (16 [1.0%] *vs* 38 [2.3%]; $p=0.002$).

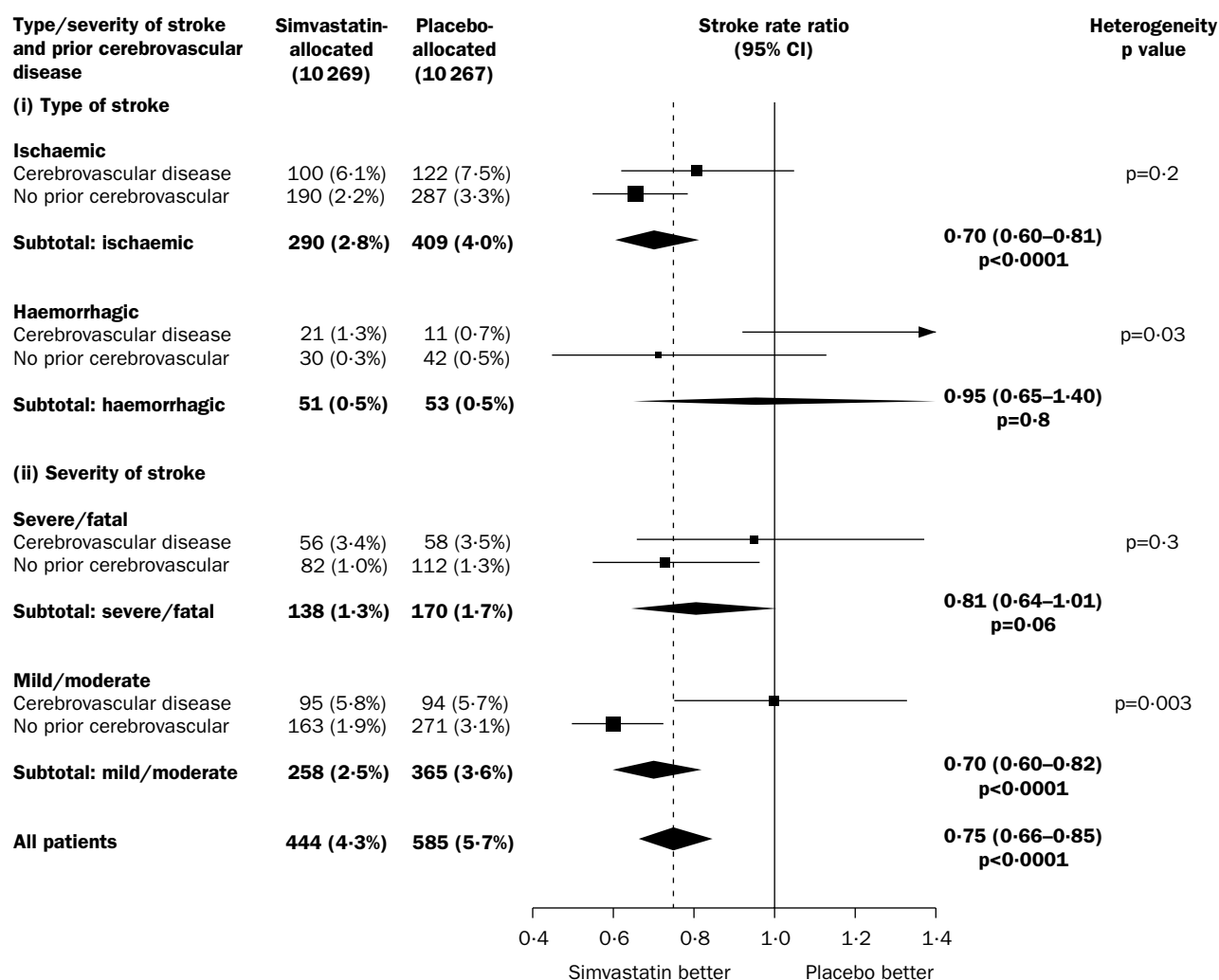


Figure 2: Effects of simvastatin allocation on type and severity of stroke in participants subdivided by prior cerebrovascular disease

Symbols and conventions as in figure 1. For stroke type, the analyses are of the numbers of participants having a first ischaemic or a first haemorrhagic stroke (with 11 having both stroke types), while those having only strokes that could not be classified are not included (prior cerebrovascular disease: 48 simvastatin vs 42 placebo; no prior cerebrovascular disease: 55 vs 92). Haemorrhagic stroke included subarachnoid haemorrhage: 12 simvastatin versus 8 placebo. For stroke severity, the analyses are of the numbers of participants having a stroke that could be classified in each of the two categories considered separately, while those with strokes of unknown severity are not included (prior cerebrovascular disease: 26 simvastatin vs 27 placebo; no prior cerebrovascular disease: 35 vs 44).

Effects on stroke type subdivided by prior cerebrovascular disease

Overall, allocation to simvastatin was associated with a highly significant 25% (15–34) proportional reduction in the incidence rate of first non-fatal or fatal stroke following randomisation (444 [4.3%] simvastatin vs 585 [5.7%] placebo; $p<0.0001$; figure 1). Few of those strokes (25 [0.2%] vs 39 [0.4%]) were preceded within 1 month by other vascular events or procedures. The reduction in stroke was due chiefly to a very definite 30% (19–40) reduction in the incidence of strokes attributed to ischaemia (290 [2.8%] vs 409 [4.0%]; $p<0.0001$; figure 2), with no significant difference in strokes attributed to haemorrhage (51 [0.5%] vs 53 [0.5%]; rate ratio [RR] 0.95 [0.65–1.40]; $p=0.8$). About 90% of the strokes of known type were ischaemic, so the strokes of unknown type (103 [1.0%] simvastatin vs 134 [1.3%] placebo) were presumably also mostly ischaemic, and there was a highly significant 28% (19–37) reduction in the incidence rate of strokes attributed to ischaemic or unknown causes (ie, “presumed ischaemic”: 393 [3.8%] vs 543 [5.3%]; $p<0.0001$).

Among participants who had pre-existing cerebrovascular disease there was no apparent reduction in the

incidence of stroke (RR 0.98 [0.79–1.22]), whereas there was a highly significant 34% (24–43; $p<0.0001$) reduction among the other high-risk participants (heterogeneity $p=0.002$; figure 1). This retrospective subgroup analysis of stroke incidence on its own was not supported by the definite benefits observed in the prespecified analysis of any major vascular event among participants with cerebrovascular disease (figures 1 and 3). Moreover, the 19% (SE 12; $p=0.1$) proportional reduction in the rate of ischaemic strokes observed among these individuals did not differ significantly from the 34% (SE 7; $p<0.0001$) reduction among the other high-risk participants studied (heterogeneity $p=0.2$; figure 2). No significant difference in haemorrhagic stroke was observed between the treatment groups in either disease category. Figure 2 also indicates that allocation to simvastatin produced about as great a proportional reduction in fatal or severely disabling strokes as in less severe strokes.

Effects on stroke subdivided by year

Among participants allocated simvastatin, there was already a non-significant trend ($p=0.3$) towards fewer strokes during the first year of follow-up and a highly

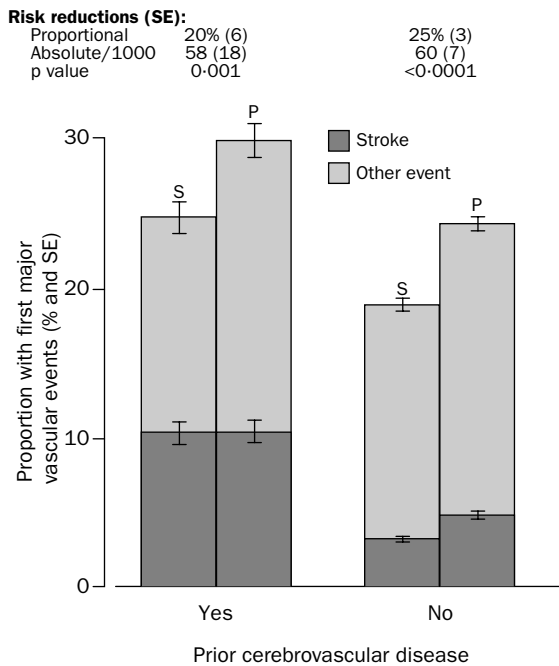


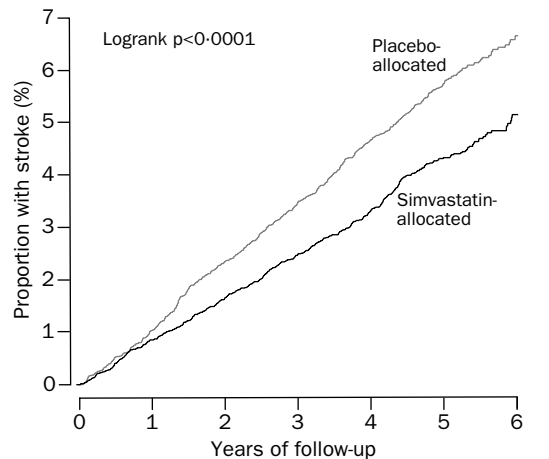
Figure 3: Absolute effects of simvastatin allocation on 5-year rates of first major vascular event and stroke among participants subdivided by prior cerebrovascular disease
 S=simvastatin-allocated; P=placebo-allocated. Dark shaded portion of each bar represents percentage having stroke during follow-up.

significant 30% (14–42; $p=0.0004$) proportional reduction by the end of the second year (figure 4). During each separate subsequent year of follow-up there were further reductions of about one-quarter in the stroke rates—even though, by the end of year 3, about one-sixth of the simvastatin-allocated participants had stopped their study treatment and about one-sixth of those allocated placebo had started statin therapy (table 2). As a consequence, whereas 5.7% of the placebo-allocated participants had one or more stroke during an average of 5 years of follow-up, only 4.3% of those allocated simvastatin did so (figures 4 and 5). Hence, the 1.0 mmol/L reduction in LDL cholesterol observed on average during HPS was typically associated with preventing 14 (SE 3) participants per 1000 from having at least one stroke during the scheduled treatment period. There were 709 first or subsequent strokes among the

Year of follow-up	Simvastatin-allocated	Placebo-allocated
1	87/10 269 (0.8%)	106/10 267 (1.0%)
2	81/10 032 (0.8%)	132/10 003 (1.3%)
3	82/9769 (0.8%)	111/9652 (1.2%)
4	81/9475 (0.9%)	111/9304 (1.2%)
5+	113/9146 (1.2%)	125/8905 (1.4%)
All	444/10 269 (4.3%)	585/10 267 (5.7%)

Figure 4: Effects of simvastatin allocation on first stroke during follow-up

Symbols and conventions as in figure 1. Analyses are of numbers of participants having a first stroke during each year of follow-up and of those still at risk of a first stroke at the start of each year.



Benefit (SE)/1000 allocated simvastatin
 2 (1) 7 (2) 10 (2) 13 (3) 14 (4) 15 (10)

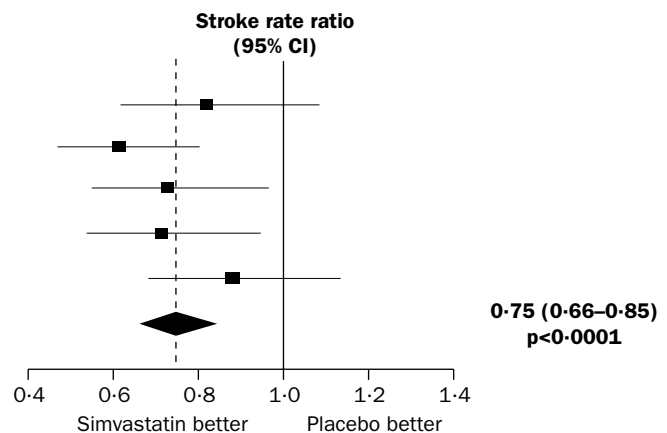
Figure 5: Life-table plot of effects of simvastatin allocation on percentages of participants having strokes

See figure 4 for numbers of participants having a first stroke during each year of follow-up. 4.3% simvastatin-allocated vs 5.7% placebo-allocated participants had strokes during average 5-year follow-up.

585 placebo-allocated patients who had strokes during the study compared with 541 strokes among the 444 simvastatin-allocated patients who had strokes. This difference corresponds to preventing 16 (4) first or subsequent strokes per 1000 patients during the 5-year period of follow-up.

Effects on stroke subdivided by other characteristics

Figure 6 indicates that the proportional reduction in the incidence rate of first stroke was about a quarter in various different circumstances (and this pattern is reinforced by the prespecified subgroup analyses of the much larger numbers of major vascular events: see webfigure at <http://image.thelancet.com/extras/04art2126webfigure.pdf>). For example, there was a 25% (12–36; $p=0.0005$) proportional reduction in the stroke rate among participants who had pre-existing coronary disease and a 26% (10–39; $p=0.002$) reduction among those with no history of coronary disease (heterogeneity $p=0.9$). Similarly, the reductions in the incidence of stroke appeared to be about the same among participants who had diabetes (24% [6–39]; $p=0.01$) and among those who did not (26% [14–36]; $p=0.0002$). The proportional reduction in the rate of strokes with allocation to simvastatin also appeared to be



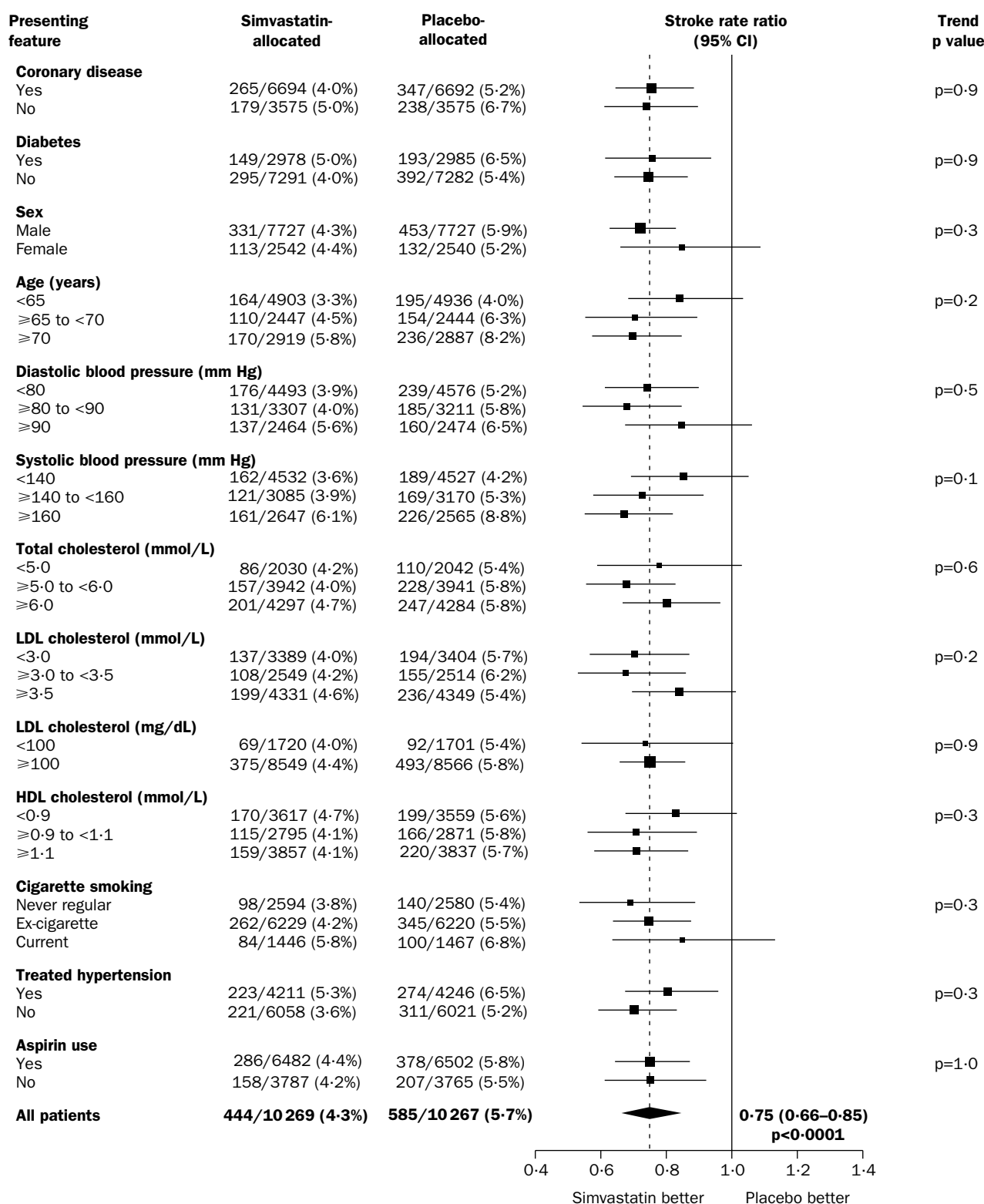


Figure 6: Effects of simvastatin allocation on first stroke during follow-up in participants subdivided by presenting features. Symbols and conventions as in figure 1. Lipid categories relate to measured values at the initial screening visit prior to starting any statin therapy. Treatment for hypertension and aspirin use recorded at entry to the study generally continued during follow-up.

about a quarter irrespective of the participants' sex, age, blood pressure, or blood lipid concentrations. Among the 6793 participants whose pretreatment measurements of LDL cholesterol were below 3.0 mmol/L (116 mg/dL), the average LDL cholesterol concentration during the trial was 2.7 mmol/L in the placebo group compared with 1.8 mmol/L in the simvastatin group (table 2). When the

analyses were restricted to those participants, there was still a highly significant 30% (13–43; $p=0.0001$) reduction in the rate of first stroke (figure 6), which reflected a significant 36% (19–49) reduction in first presumed ischaemic stroke (115 [3.4%] simvastatin *vs* 178 [5.2%] placebo; $p=0.0002$) and no apparent excess of first haemorrhagic stroke (22 [0.6%] *vs* 21 [0.6%]). Indeed, even among the

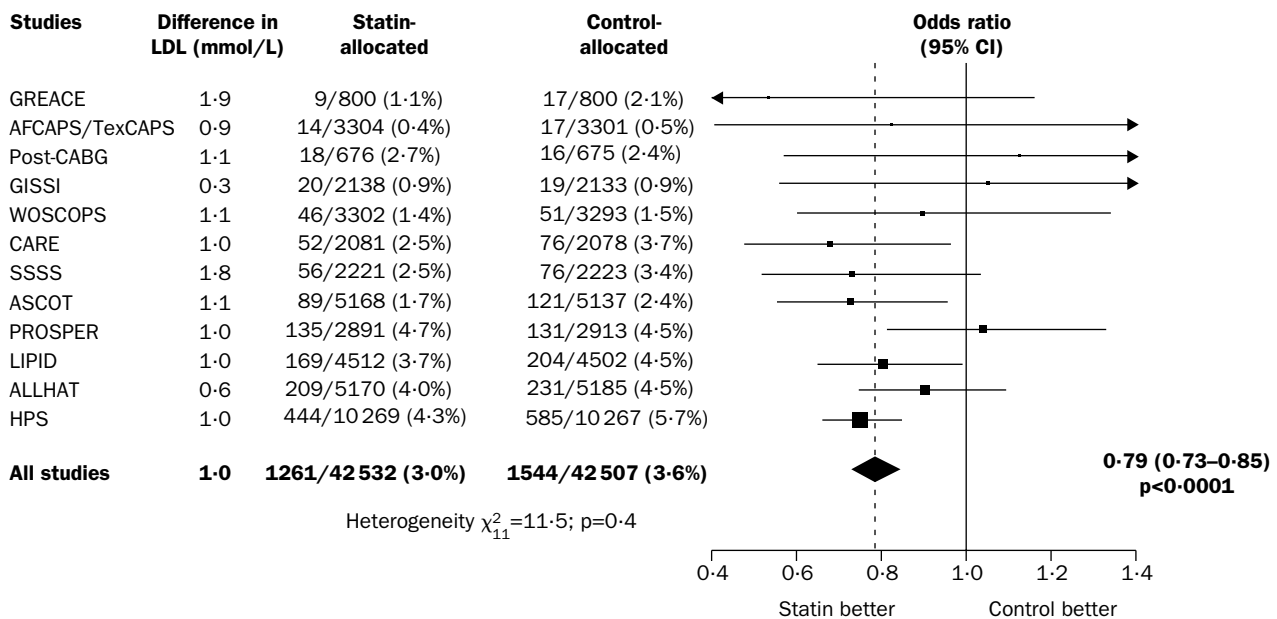


Figure 7: Meta-analysis of effects of statin allocation on stroke in major randomised trials

Symbols and conventions as in figure 1. LDL cholesterol differences refer to estimated average differences between statin-allocated and placebo-allocated patients during the scheduled treatment period (ie, intention-to-treat). Overall result for all studies is weighted according to estimated average LDL difference and number of strokes in each contributing trial.

3421 patients presenting with LDL below 2.6 mmol/L (100 mg/dL), the observed reduction in the rate of stroke (26% [SE 14]; $p=0.05$) was similar to that seen among participants recruited with higher LDL cholesterol concentrations (25% [SE 6]; $p<0.0001$). The absolute risk of stroke increased with increasing age and blood pressure, and consequently so too did the absolute reduction in stroke risk produced by allocation to simvastatin (figure 6). The beneficial effects of simvastatin on stroke were additional to those of antihypertensive treatment and of aspirin use at study entry. Blood pressure levels fell during follow-up, but allocation to simvastatin was not associated with significant differences in these falls in systolic (-7.6 mm Hg simvastatin *vs* -7.1 mm Hg placebo; difference -0.5 [SE 0.4] mm Hg) or diastolic pressure (-4.5 mm Hg *vs* -4.6 mm Hg; difference 0.1 [SE 0.2] mm Hg).

Effects on other neurological outcomes

Carotid events

In addition to effects on stroke, there was a significant reduction in the numbers of participants who, although not suffering a stroke during the trial, had at least one episode of transient cerebral ischaemia (204 [2.0%] simvastatin *vs* 250 [2.4%] placebo; $p=0.02$). Non-significantly fewer individuals had retinal artery occlusions (9 [0.1%] *vs* 16 [0.2%]), while similar numbers had episodes of amaurosis fugax (11 [0.1%] *vs* 9 [0.1%]). Among participants with pre-existing cerebrovascular disease there was no apparent reduction in the numbers of patients who reported transient cerebral ischaemic attacks (irrespective of whether any stroke also occurred) during the scheduled treatment period (107 [6.5%] *vs* 112 [6.9%]), whereas there was a highly significant reduction among all other participants (153 [1.8%] *vs* 203 [2.4%]; $p=0.006$).

Cognitive function

Based on observational studies involving just a few years of treatment, it has been suggested that statin use might slow cognitive decline.^{33,34} On the other hand, there have been case reports that statin therapy might be associated with

memory loss.³⁵ Reliable unbiased assessment of the causal nature of such observations is likely to require large-scale randomised placebo-controlled trials of long-term statin therapy.³⁶ The modified Telephone Interview for Cognitive Status (TICS-m) questionnaire is well-validated,³⁷ with a high proportion of the total score assigned to memory. In HPS, TICS-m was administered to participants during their final follow-up (89% in clinic and 11% by telephone) after a mean of 5.3 years of scheduled treatment. A TICS-m score below 22 out of 39 was prespecified as indicative of some cognitive impairment and, as would be expected, was more common among older individuals and those who had a previous stroke.²⁷ No significant differences were observed between the treatment groups in the percentages of patients classified as cognitively impaired (23.7% simvastatin-allocated *vs* 24.2% placebo-allocated), and similar numbers were reported to have developed dementia during follow-up (31 [0.3%] *vs* 31 [0.3%]). Nor were there any significant differences between the treatment groups in the overall mean TICS-m score (24.08 *vs* 24.06; difference 0.02 [SE 0.07]), in the scores for any of the four separate domains of TICS-m (including the one representing memory: 8.87 *vs* 8.89; difference -0.03 [SE 0.05]), or in a separate "verbal fluency" score (21.51 *vs* 21.56; difference -0.05 [SE 0.12]).³⁷

Neuropathy

Various case reports and observational studies have raised the possibility that statins might have adverse effects on the peripheral nervous system.^{38,39} In the largest of those non-randomised studies, nine of 166 patients with a diagnosis of idiopathic polyneuropathy had taken comparatively low statin doses (eg, an average of 15 mg simvastatin daily or the equivalent of another statin) for a median of 2.8 years, and the relative risk associated with statin use was 3.7 (95% CI 1.8–7.6).³⁹ But, despite 10 000 participants in HPS having been randomly allocated to receive 40 mg simvastatin daily for an average of 5 years, no significant excess of peripheral neuropathy was reported and the absolute 5-year risks were low (11 [0.1%] simvastatin *vs* 8 [0.1%] placebo). More

simvastatin-allocated patients did report cranial nerve problems (18 [0.2%] *vs* 7 [0.1%]), but this may reflect the large number of retrospective analyses performed, and there was no apparent excess of reports of spinal cord problems (5 [0.0%] *vs* 6 [0.1%]) or of peripheral nerve compression or surgery (99 [1.0%] *vs* 84 [0.8%]).

Discussion

Due to its large size and the types of high-risk patient studied, much larger numbers of participants suffered a stroke during HPS than in any other randomised trial of cholesterol-lowering therapy. Consequently, the present study is able to resolve many of the remaining uncertainties about the effects of statin therapy on the incidence of stroke.^{24,25} In particular, it shows that cholesterol-lowering statin therapy rapidly produces a definite and substantial reduction in ischaemic stroke, irrespective of the patient's age, sex, or blood lipid concentrations when treatment is initiated. It also demonstrates that statin therapy reduces the risk of major vascular events among people who have previously had a stroke or other cerebrovascular event, even if they do not already have manifest coronary disease. These results have important implications for revising national and international treatment guidelines which do not currently take into account cerebrovascular disease risk reduction when considering the initiation of statin therapy.^{40,41}

When the published results from the large-scale randomised statin trials are now considered together,^{13-18,42-46} an average reduction in LDL cholesterol of about 1.0 mmol/L (39 mg/dL) is associated with a 21% (95% CI 15-27) proportional reduction in the incidence of stroke (figure 7). HPS demonstrates that this benefit is largely due to a definite and substantial reduction in ischaemic stroke, with additional reductions in transient cerebral ischaemic attacks and in the need for carotid endarterectomy or angioplasty. It had been reported from non-randomised observational studies that lower blood cholesterol concentrations might be associated with higher risks of haemorrhagic stroke.⁸⁻¹¹ But, lowering cholesterol substantially with simvastatin did not produce any apparent excess of haemorrhagic stroke in HPS, even among the 6793 participants with pretreatment LDL cholesterol concentrations below 3.0 mmol/L who had those levels reduced to an average of about 1.8 mmol/L. There were relatively few haemorrhagic strokes in HPS, and still smaller numbers have been reported so far from the other statin trials (chiefly LIPID and CARE: 19 pravastatin *vs* 15 placebo⁴⁷). Consequently, although the present results provide some refutation of previous concerns about haemorrhagic stroke, this issue will be most reliably addressed by the prospectively planned meta-analysis that is now ongoing of the much larger numbers of type-specific strokes recorded in all such trials.⁴⁸

Based on fewer than 300 strokes in the PROSPER trial, it had been suggested that any stroke benefit with statin therapy does not begin to emerge until at least 3 years after the initiation of treatment, but that the coronary risk reduction emerges much earlier (implying different mechanisms of action).⁴³ By contrast, based on over 1000 strokes in HPS, it is clear that the beneficial effect on stroke emerges rapidly, with a highly significant reduction within 2 years of starting simvastatin (which is similar to the pattern seen for coronary events²⁷). The continuing divergence in stroke incidence during each year of treatment also suggests that even more prolonged statin therapy would eventually produce even larger absolute reductions in stroke risk. In HPS, a 1 mmol/L reduction in LDL cholesterol from about 4 mmol/L to about 3 mmol/L

reduced the risks of stroke and of other major vascular events by about one-quarter, and so too did reducing it from about 3 mmol/L to about 2 mmol/L (as might be expected from the approximately loglinear association in observational studies between occlusive vascular disease rates and usual LDL cholesterol concentrations^{24,41}). These findings strongly support the original hypothesis of the study that any thresholds below which lowering LDL cholesterol does not safely reduce risk are at much lower concentrations (eg, below 2 mmol/L [77 mg/dL] of LDL cholesterol or 3.5 mmol/L [135 mg/dL] of total cholesterol) than are typically seen in Western populations. Current guidelines could, therefore, inadvertently lead to substantial under-treatment of high-risk patients who present below, or close to, particular targets for LDL cholesterol concentrations.⁴⁹ Moreover, the clear demonstration of a reduction in ischaemic stroke, without any evidence of an adverse effect on haemorrhagic stroke, indicates that statin therapy may safely produce substantial benefits among high-risk individuals in populations (such as China) where the risks of ischaemic stroke are relatively high, but LDL cholesterol concentrations and coronary heart disease risk are relatively low.^{3,29}

Most participants in previous statin trials did not have a history of cerebrovascular disease, and results were not typically reported separately for such patients in those trials. By contrast, HPS involved 3280 people who had had a non-disabling ischaemic stroke, transient cerebral ischaemic attack or carotid artery procedure prior to randomisation. Among those patients, allocation to receive simvastatin was not associated with any apparent reduction in the stroke rate during the scheduled treatment period (although there was a non-significant trend towards fewer ischaemic strokes). This subgroup analysis was not prespecified, and it is based on only about 300 strokes among participants with prior cerebrovascular disease. Consequently, given the clear reductions in stroke risk among other high-risk participants, the apparent lack of effect on stroke in this subgroup considered on its own may well reflect the play of chance. Current trials will provide further information about the prevention of stroke recurrence with cholesterol-lowering therapy,⁵⁰ especially when considered in conjunction with HPS and the other large statin trials in the prospectively planned meta-analysis.⁴⁸ But, the highly significant reduction in major vascular events among participants in HPS with pre-existing cerebrovascular disease (figure 3)—irrespective of the presence of coronary disease—does already provide compelling evidence that such patients can gain substantial benefits from statin therapy.

During HPS, an average of about a sixth of the participants allocated 40 mg simvastatin daily had stopped taking statin therapy, and about a sixth of those allocated placebo had started to take a statin. As a consequence, the average difference in LDL cholesterol of about 1 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 the incidence of strokes 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 stroke and of other major vascular events by about a third. Given that stroke is one of the major causes of mortality and major morbidity worldwide,^{29,51} these findings indicate that statin

therapy should now be considered routinely for all patients at high risk of stroke, irrespective of their initial cholesterol concentrations or the presence of coronary disease.

MRC/BHF Heart Protection Study Collaborative Group

Collaborators—listed at

<http://image.thelancet.com/extras/04art2126webextra.pdf>.

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Conflict of interest statement

The Clinical Trial Service Unit has a staff policy of not accepting honoraria or other payments 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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