Articles

# MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

*Heart Protection Study Collaborative Group**


## Summary

**Background** Throughout the usual LDL cholesterol range in Western populations, lower blood concentrations are associated with lower cardiovascular disease risk. In such populations, therefore, reducing LDL cholesterol may reduce the development of vascular disease, largely irrespective of initial cholesterol concentrations.

**Methods** 20 536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%). Analyses are of the first occurrence of particular events, and compare all simvastatin-allocated versus all placebo-allocated participants. These "intention-to-treat" comparisons assess the effects of about two-thirds (85% minus 17%) taking a statin during the scheduled 5-year treatment period, which yielded an average difference in LDL cholesterol of 1·0 mmol/L (about two-thirds of the effect of actual use of 40 mg simvastatin daily). Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.

**Findings** All-cause mortality was significantly reduced (1328 [12·9%] deaths among 10 269 allocated simvastatin versus 1507 [14·7%] among 10 267 allocated placebo; p=0·0003), due to a highly significant 18% (SE 5) proportional reduction in the coronary death rate (587 [5·7%] *vs* 707 [6·9%]; p=0·0005), a marginally significant reduction in other vascular deaths (194 [1·9%] *vs* 230 [2·2%]; p=0·07), and a non-significant reduction in non-vascular deaths (547 [5·3%] *vs* 570 [5·6%]; p=0·4). There were highly significant reductions of about one-quarter in the first event rate for non-fatal myocardial infarction or coronary death (898 [8·7%] *vs* 1212 [11·8%]; p<0·0001), for non-fatal or fatal stroke (444 [4·3%] *vs* 585 [5·7%]; p<0·0001), and for coronary or non-coronary revascularisation (939 [9·1%] *vs* 1205 [11·7%]; p<0·0001). For the first occurrence of any of these major vascular events, there was a definite 24% (SE 3; 95% CI 19–28) reduction in the event rate (2033 [19·8%] *vs* 2585 [25·2%] affected individuals; p<0·0001). During the first year the reduction in major vascular events was not significant, but subsequently it was highly significant during each separate year. The proportional reduction in the event rate was similar (and significant) in each subcategory of participant studied, including: those without diagnosed coronary disease who had cerebrovascular disease, or had peripheral artery disease, or had diabetes; men and, separately, women; those aged either under or over 70 years at entry; and—most notably—even those who presented with LDL cholesterol below 3·0 mmol/L (116 mg/dL), or total cholesterol below 5·0 mmol/L (193 mg/dL). The benefits of simvastatin were additional to those of other cardioprotective treatments. The annual excess risk of myopathy with this regimen was about 0·01%. There were no significant adverse effects on cancer incidence or on hospitalisation for any other non-vascular cause.

**Interpretation** Adding simvastatin to existing treatments safely produces substantial additional benefits for a wide range of high-risk patients, irrespective of their initial cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rates of myocardial infarction, of stroke, and of revascularisation by about one-quarter. After making allowance for non-compliance, actual use of this regimen would probably reduce these rates by about one-third. Hence, among the many types of high-risk individual studied, 5 years of simvastatin would prevent about 70–100 people per 1000 from suffering at least one of these major vascular events (and longer treatment should produce further benefit). The size of the 5-year benefit depends chiefly on such individuals' overall risk of major vascular events, rather than on their blood lipid concentrations alone.


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*See Commentary page 2*

## Introduction

Observational studies in different populations indicate a continuous positive relationship between coronary heart disease risk and blood LDL cholesterol concentration that extends well below the range currently seen in Western populations, without any definite "threshold" below which a lower concentration is not associated with lower risk.[1–5] 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 usual LDL cholesterol concentration is similar throughout the range that has been studied. Hence, the absolute size of the risk reduction produced by lowering LDL cholesterol may be determined more by an individual's overall risk of cardiovascular disease than by just their initial blood lipid concentrations. If this is the case, then the benefits of treatment may be greatest in those who, as a consequence of their previous medical history (eg, occlusive arterial disease or diabetes) or some other factors (eg, age), are at greatest risk.

Recently, large randomised trials have shown that lowering LDL cholesterol with 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors

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("statins") reduces coronary mortality and morbidity in some types of high-risk patient.[6–11] Typically in those trials, an average reduction in LDL cholesterol of about 1 mmol/L maintained for about 5 years produced a reduction in non-fatal myocardial infarction and coronary death of about one-quarter (which is about half the effect associated epidemiologically with a long-term difference of 1 mmol/L in people without diagnosed vascular disease[2,4]). But, even after those trials, there was still only limited evidence about the effects of such treatment in many specific types of high-risk patient—in particular, those without diagnosed coronary disease who have diabetes or non-coronary occlusive arterial disease; those who are female or elderly; and those with below-average LDL cholesterol concentrations for Western populations.[12-15] Moreover, although those trials did not find any excess of non-coronary deaths or major morbidity, further evidence was still needed of the long-term effects of lowering LDL cholesterol on cause-specific mortality and on cancers of particular sites.[16-22]

The Heart Protection Study aimed to help resolve some of those remaining uncertainties by assessing the long-term effects of cholesterol-lowering therapy on vascular and non-vascular mortality and major morbidity in a wide range of circumstances. To do this reliably, it included large numbers of people at substantial risk of death from both vascular and other causes, and involved a substantial LDL cholesterol reduction maintained for several years.

## Patients and methods

Details of the study objectives, design, and methods have been reported previously[12,23] (including the protocol on the study website: www.hpsinfo.org), and are summarised below. As well as comparing the effects of cholesterol-lowering therapy versus matching placebo in 20 536 randomised participants (which is the subject of the present report), a "2×2 factorial" design was used to allow the separate assessment of antioxidant vitamin supplementation (see accompanying report[24]).

### *Eligibility*

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 were considered to be at substantial 5-year risk of death from coronary heart disease because of a past medical history of: (i) coronary disease (ie, myocardial infarction, unstable or stable angina, coronary artery bypass graft, or angioplasty); or (ii) occlusive disease of non-coronary arteries (ie, non-disabling stroke not thought to be haemorrhagic, transient cerebral ischaemia, leg artery stenosis [eg, intermittent claudication], carotid endarterectomy, other arterial surgery or angioplasty); or (iii) diabetes mellitus (whether type 1 or type 2[12,25]); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories). No upper limit of blood cholesterol concentration for inclusion was imposed since there were people (such as those who had not previously had a myocardial infarction, or were female or elderly) in whom many clinicians were substantially uncertain as to the benefits of lowering even an "elevated" cholesterol. But, anyone in whom statin therapy was considered by their own doctor to be clearly indicated was not to be randomised.

In addition, people were ineligible if they had: chronic liver disease (cirrhosis or hepatitis) or evidence of abnormal liver function (eg, alanine aminotransferase >67 IU/L [1·5 times the central laboratory upper limit of normal: ULN]); severe renal disease or evidence of impaired renal function (creatinine >200 μmol/L); inflammatory muscle disease (eg, dermatomyositis or polymyositis) or evidence of muscle problems (creatine kinase >750 IU/L [3×ULN]); concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential (premenopausal woman not sterilised or using reliable contraception); severe heart failure; some life-threatening condition other than vascular disease or diabetes (eg, severe chronic airways disease or any cancer other than non-melanoma skin cancer); or conditions that might limit long-term compliance (eg, severely disabling stroke, dementia, or psychiatric disorder).

### *Recruitment*

Medical collaborators from 69 UK hospitals appointed senior nurses to run special clinics for the study (see Acknowledgments) and, with the help of the coordinating centre, obtained local ethics committee approval. Records of patient discharges and of special wards or clinics 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. Those individuals who appeared eligible for the study were given detailed information about it, and asked for their written agreement to participate.

Potentially eligible people entered a prerandomisation "run-in" phase, which was intended chiefly to limit subsequent randomisation to those likely to take the randomly allocated study treatment for at least 5 years.[26] Run-in treatment involved 4 weeks of placebo (to allow review of liver enzymes, creatinine, and creatine kinase by the central laboratory before starting any simvastatin) followed by 4–6 weeks of a fixed dose of 40 mg simvastatin daily (to allow a prerandomisation assessment of the LDL-lowering "responsiveness" of each individual: see Results). The general practitioner was informed during the run-in of their patient's lipid profile, including LDL cholesterol measured directly (rather than estimated from the Friedewald equation[27]) which is accurate in non-fasting samples.[28,29] If the general practitioner considered there to be a clear indication for (or, conversely, a clear contraindication to) statin therapy then that person was not to be offered randomisation. Compliant individuals who did not have a major vascular event or other serious problem during the run-in, and agreed to participate in the study for several years, were randomly allocated to receive 40 mg simvastatin daily or matching placebo tablets in specially prepared calendar packs (and separately, using a 2×2 factorial design, antioxidant vitamins [600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily] or matching placebo capsules[24]). The central telephone randomisation system used a minimisation algorithm[30] to balance the treatment groups with respect to eligibility criteria and other major prognostic factors.

### *Follow-up*

Following randomisation between July, 1994, and May, 1997, participants were to be seen in the study clinics for routine follow-up checks and blood safety monitoring at 4, 8, and 12 months and then 6-monthly until the final follow-up visits between May and October, 2001. Those who became unable or unwilling to attend the clinics 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), but their allocated study simvastatin or matching placebo tablets were to be stopped (since blood safety monitoring could not be continued). Compliance with study treatment was assessed at each follow-up by reviewing the calendar-packed tablets remaining and, for those who had stopped, the reasons for doing so were sought. Participants and their general practitioners were advised of results emerging from other relevant studies,[6-11] and encouraged to use a non-study statin if they considered that it had become indicated. During the early part of the study, participants who were prescribed a non-study statin were routinely advised to stop their study simvastatin or placebo tablets. But, that policy was changed in early 1998 (when 80 mg simvastatin daily became a licensed dose) to allow continuation of the study tablets along with non-study statin regimens not exceeding, in lipid-lowering potency, the equivalent of about 40 mg simvastatin daily. 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 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 in non-fasting blood collected from a selected sample of about 5% 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. 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 non-compliance).

Information was recorded at each follow-up of any suspected myocardial infarction, stroke, vascular procedure, cancer or other serious adverse experience, and of the main reasons for all other hospital admissions (including day cases). Further details were sought from the participant's general practitioner (plus, if considered necessary for coding, from any relevant hospital records) about all reports that might relate to major vascular events, cancers, or deaths, and from the UK national registries about the sites of any registered cancers and the certified causes of any deaths. All such information was reviewed by coordinating centre clinical staff who were kept unaware of the study treatment allocation, and events were coded according to prespecified criteria. Analyses were to be based on confirmed plus unrefuted reports of events, with definite confirmation for 98% of the myocardial infarctions, strokes, and revascularisations that were included. Confirmation of myocardial infarction required evidence of either: (i) two or more of: (a) typical symptoms, (b) diagnostic electrocardiographic changes, and (c) diagnostic elevations of cardiac enzyme concentrations; or (ii) necropsy findings of myocardial infarction that corresponded to symptom onset. ("Silent" myocardial infarctions were not to be included.) Deaths attributed to myocardial infarction, other coronary disease (including heart failure due to coronary disease), and sudden or unexpected deaths (without post-mortem evidence of another cause) were classified as coronary death. Stroke was defined as rapid (or uncertain) onset of focal or global neurological deficit lasting more than 24 h or leading to death, with clinical evidence supplemented by neurological imaging or necropsy required to classify strokes as probably ischaemic or probably haemorrhagic. (Subarachnoid haemorrhage was to be included, but subdural haematoma or transient cerebral ischaemia was not.) The severity of the stroke was classified as "mild" when there seemed to be no interference with lifestyle, "moderate" when some help was needed for everyday activities, "severe" when constant care and attention was needed, and "fatal" when death occurred within about 1 month. Amputations were to be included in non-coronary revascularisation since, in this population, most were expected to be due to occlusive vascular disease. Cancers were classified according to their primary anatomical site (rather than their histology), except that skin cancers were subclassified as melanoma or non-melanoma.

### *Statistical analysis*

The data analysis plan was prespecified either in the original protocol[23] or in amendments (see study website) made before any analyses of the effects of treatment on clinical outcomes were available to the Steering Committee. All 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, they were "intention-to-treat" analyses).[31] The logrank analysis yielded the average event or death rate ratio (with the proportional reduction in this ratio expressed as a percentage) and the test of statistical significance (two-sided p value). The primary comparisons were of the effects of allocation to simvastatin on deaths from all causes, from coronary heart disease, and from all other causes. Secondary comparisons were of the effects: (i) on specific non-coronary causes of death; (ii) on "major coronary events" (defined as non-fatal myocardial infarction or death from coronary disease), and on "major vascular events" (defined as major coronary events, strokes of any type, and coronary or non-coronary revascularisations), during the first 2 years and during the later years of scheduled treatment; and (iii) on non-fatal or fatal strokes of any type. Other secondary comparisons included the effects on major coronary events, and on major vascular events, in different subcategories of prior disease and in other major subcategories determined at study entry. Tests for heterogeneity or, if more appropriate, trend were to be used to assess whether the proportional effects observed in specific subcategories differed clearly from the overall effects (after due allowance for multiple comparisons). In addition, several tertiary outcomes were prespecified (including site-specific cancer, cerebral haemorrhage, vascular procedures, hospitalisation for angina and for fractures, cognitive impairment, and loss of respiratory function), again with due allowance in interpretation to be made for the exploratory and, perhaps, data-dependent nature of these, and the many other, analyses that might be performed.[31,32]

Based on previous studies in similar populations, it was estimated that there might be about 1500 coronary deaths, plus similar numbers of non-fatal myocardial infarctions, among 20 000 such patients followed for an average of 5 years.[23] If so, and if cholesterol-lowering therapy reduced 5-year coronary heart disease mortality by about 25% and all-cause mortality by about 15%, then a study of this size with good compliance would have an excellent chance of demonstrating such effects at convincing levels of statistical significance (ie, >90% power to achieve $p<0{\cdot}01$).[23,33] Moreover, in any particular category of these high-risk individuals, randomisation of at least a few thousand would allow reliable assessment of

a reduction of a quarter in the incidence rate of major coronary events and, particularly, of major vascular events (with about 5000 participants expected to have major coronary events, strokes, or revascularisations). There were also expected to be more than 1000 deaths from causes other than coronary disease and more than 1000 new cancers during the scheduled follow-up, which would allow reasonably reliable assessment of the 5-year effects of treatment on the main non-coronary causes of death and on the main types of cancer (especially in conjunction with results from the other large statin trials[34]).

During the study, interim analyses of mortality and of other major events were supplied at least annually to the independent Data Monitoring Committee. In the light of those analyses and the results of any other relevant trials, the Data Monitoring Committee was to advise the Steering Committee if, in their view, the randomised comparisons in the study had provided both (i) "proof beyond reasonable doubt" that, either for all participants or for some specific types of participant, use of statin therapy was clearly indicated or clearly contraindicated in terms of a net difference in all-cause mortality; and (ii) evidence that might reasonably be expected to influence materially the management of patients by many clinicians who were already aware of any other available trial results. As this did not happen, the Steering Committee, the collaborators, the funding agencies, and the coordinating centre staff (except those supplying the confidential analyses) remained unaware of the results on mortality and major morbidity until completion of the scheduled treatment period.

*Role of the funding source*

The study was designed, conducted, analysed, and interpreted by the investigators entirely independently of all funding sources.

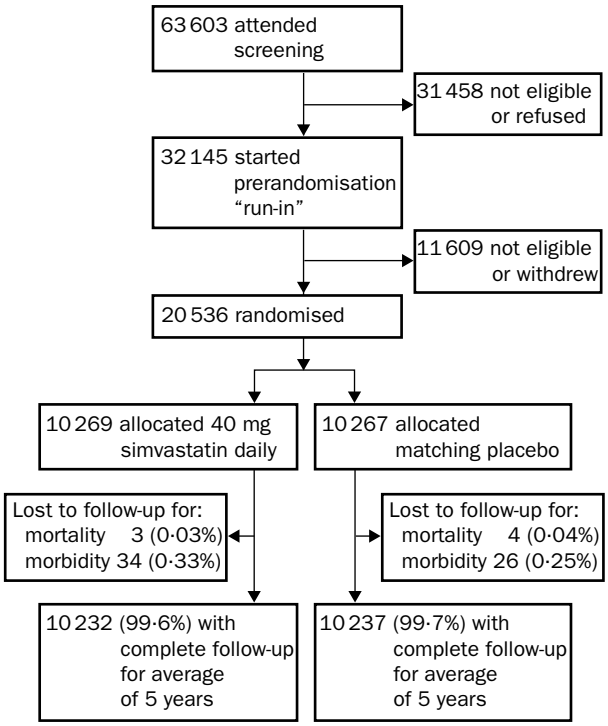



Figure 1: **Trial profile**
Numbers lost to follow-up relate to those without information to the end of the scheduled treatment period for mortality (as well as morbidity) and for morbidity alone.

## Results

*Patient enrolment*

63 603 people attended the initial screening clinic visit, and 32 145 were potentially eligible and agreed to enter the prerandomisation run-in phase of the study (figure 1).[23] Of those who entered run-in, 36% were not subsequently randomised: 26% chose not to enter the trial or did not seem likely to be compliant for 5 years, 5% were considered by their own doctors to have a clear indication for (or, rarely, contraindication to) statin therapy, 3% had elevated concentrations of liver enzymes, creatinine, or creatine kinase in their pretreatment screening blood sample, 2% attributed various problems to the run-in treatment (with about half doing so before starting any simvastatin), 1% had non-fasting screening total cholesterol below 3·5 mmol/L, 0·3% reported having myocardial infarction, stroke, or hospitalisation for angina during run-in, and two (0·01%) developed myopathy. Nobody was excluded because of elevations in liver enzymes during run-in: central laboratory assay of blood collected at the randomisation visit did subsequently identify alanine aminotransferase >4×ULN in two people who had been randomised, but both continued in the study and those elevations were not persistent.

A total of 20 536 individuals (15 454 men and 5082 women) were randomised, with 5806 aged at least 70 years at study entry. Previous myocardial infarction was reported by 8510 (41% of those randomised), some other history of coronary disease by 4876 (24%), and no history of coronary disease by 7150 (35%). Among the 7150 participants without diagnosed coronary disease, 1820 had cerebrovascular disease, 2701 had peripheral arterial disease, and 3982 had diabetes mellitus (with some having more than one of these three conditions), whereas among the 13 386 with known coronary disease, 1460, 4047, and 1981, respectively, had these conditions (again, with some "non-additivity" of these groups: see subcategory figure below). Although treated hypertension was recorded in 8457 (41%) participants, only 237 (1%) were included on the basis of hypertension alone. At the initial screening visit before any statin treatment had started, those participants who were subsequently randomised had mean non-fasting blood concentrations of total cholesterol of 5·9 mmol/L (SD 1·0), directly measured LDL cholesterol of 3·4 mmol/L (0·8), HDL-cholesterol of 1·06 mmol/L (0·33), triglycerides of 2·1 mmol/L (1·4), apolipoprotein $A_1$ of 1·20 g/L (0·22), and apolipoprotein B of 1·14 g/L (0·23). The large size of the study (and the use of minimisation) produced good balance between the treatment groups for the main prerandomisation 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 5 years for all randomised participants: 5·3 years for those who survived

| Follow-up (years) | Simvastatin-allocated | Placebo-allocated |
|---|---|---|
| 1 | 8994/10 107 (89%) | 389/10 088 (4%) |
| 2 | 8457/9909 (85%) | 889/9826 (9%) |
| 3 | 8122/9664 (84%) | 1608/9563 (17%) |
| 4 | 7764/9388 (83%) | 2262/9241 (24%) |
| 5 | 6058/7370 (82%) | 2345/7225 (32%) |
| **Study average (SE)** | 85% (0·1) | 17% (0·1) |

For missing follow-up, non-compliance is assumed. Restriction of this analysis to those who had not yet suffered a major vascular event did not materially alter the estimated average use of statin therapy: 86% simvastatin-allocated versus 15% placebo-allocated (71% difference).

Table 1: **Compliance with study simvastatin (≥80% taken) and/or use of non-study statin during follow-up**

| Follow-up (years) | Mean (SE) difference in concentrations (simvastatin minus placebo)* | | | | | |
|---|---|---|---|---|---|---|
| | Total cholesterol | LDL cholesterol | HDL cholesterol | Triglycerides | Apolipoprotein $A_1$ | Apolipoprotein B |
| 1 | –1·7 (0·08) | –1·3 (0·06) | 0·02 (0·02) | –0·4 (0·08) | 0·020 (0·015) | –0·36 (0·02) |
| 3 | –1·2 (0·09) | –0·9 (0·08) | 0·02 (0·03) | –0·4 (0·11) | 0·001 (0·016) | –0·29 (0·03) |
| 5 | –0·8 (0·03) | –0·7 (0·03) | 0·02 (0·01) | –0·2 (0·04) | 0·004 (0·026) | –0·18 (0·04) |
| **Study average** | –1·2 (0·02) | –1·0 (0·02) | 0·03 (0·01) | –0·3 (0·03) | 0·010 (0·007) | –0·28 (0·01) |

*Intention-to-treat comparisons, with missing data imputed from initial pretreatment screening values; mmol/L for total, LDL, HDL, and triglycerides, and g/L for apolipoproteins. Similar average differences with simvastatin versus placebo allocation were observed in the presence and absence of the study vitamins for total cholesterol (–1·20 [0·03] in those allocated vitamins and –1·18 [0·03] in those allocated matching placebo), for LDL cholesterol (–0·95 [0·02] and –0·97 [0·02]), for HDL cholesterol (0·02 [0·01] and 0·04 [0·01]), and for triglycerides (–0·31 [0·04] and –0·26 [0·04]).

Table 2: **Differences in plasma concentrations of lipids during follow-up**

to the scheduled end of study treatment and about half that for those who did not (yielding 51 121 person-years among all those allocated simvastatin and 50 664 among all those allocated placebo). 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 (with only about 2% of participants reported to be taking some, but less than 80%, of the treatment). Participants allocated placebo were more likely to be prescribed a non-study statin by their own doctors, presumably because their cholesterol concentrations during follow-up tended to be higher. (Of all 4002 participants taking a non-study statin at the final follow-up, 53% were using simvastatin, 28% atorvastatin, 10% pravastatin, 5% cerivastatin, and 4% fluvastatin.) Among participants allocated 40 mg simvastatin daily, 89% at the end of the first year of follow-up, and 82% at the end of the fifth year, remained compliant with their study tablets or were taking a non-study statin, yielding an average statin use during the scheduled treatment period of 85% (82% on their allocated simvastatin, 3% on non-study statin alone, and 2% on both: table 1). By contrast, among those allocated placebo, 4% at the end of the first year of follow-up, but 32% at the end of the fifth year, were taking non-study statin therapy, yielding an average of 17%. Hence, the average difference between these groups in the percentage actually taking a statin was about 67% (85% minus 17%), and a similar difference was found among those who had not yet suffered a major vascular event (see footnote to table 1). As a consequence, the intention-to-treat comparisons in this report assess the effects of about two-thirds of simvastatin-allocated participants actually taking 40 mg simvastatin daily.

Table 2 shows the blood lipid differences between those allocated simvastatin and those allocated placebo, with an average difference in LDL cholesterol during the study of 1·0 mmol/L being produced by the average difference of two-thirds in statin use (whereas actual use of 40 mg simvastatin daily would reduce LDL cholesterol by an average of about 1·5 mmol/L in this population). By contrast with the findings of a smaller study,[35] the antioxidant vitamins studied[24] did not appreciably modify the effects of simvastatin on plasma lipid concentrations (see table 2 footnote). Table 3 subdivides the average use of study or non-study statin, and the average plasma concentrations of LDL cholesterol, by various presenting features. Non-study statin use in the placebo group was more common among those who had diagnosed coronary disease at entry, were younger, or, particularly, had higher pretreatment plasma concentrations of total or LDL cholesterol. In each subcategory in table 3, however, the average 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 (0·8–1·1 mmol/L).

| 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** | | | | | | |
| Prior MI | 87% | 22% | 65% | 2·3 | 3·2 | –0·9 |
| Other CHD | 85% | 18% | 67% | 2·3 | 3·3 | –1·0 |
| No CHD | 83% | 11% | 71% | 2·3 | 3·3 | –1·0 |
| **Sex** | | | | | | |
| Male | 86% | 18% | 68% | 2·2 | 3·2 | –1·0 |
| Female | 82% | 16% | 65% | 2·5 | 3·4 | –0·9 |
| **Age (years)** | | | | | | |
| <65 | 85% | 20% | 64% | 2·4 | 3·2 | –0·9 |
| ⩾65<70 | 87% | 18% | 69% | 2·2 | 3·3 | –1·0 |
| ⩾70 | 84% | 12% | 72% | 2·2 | 3·3 | –1·1 |
| **Total cholesterol (mmol/L)** | | | | | | |
| <5·0 | 83% | 5% | 78% | 1·8 | 2·6 | –0·9 |
| ⩾5·0<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<3·5 | 86% | 16% | 69% | 2·2 | 3·2 | –1·0 |
| ⩾3·5 | 86% | 26% | 60% | 2·7 | 3·7 | –1·0 |
| **Prerandomisation LDL response** | | | | | | |
| Smaller (<38%) | 83% | 18% | 64% | 2·5 | 3·3 | –0·8 |
| Average | 86% | 18% | 68% | 2·3 | 3·3 | –1·0 |
| Larger (⩾48%) | 86% | 16% | 70% | 2·1 | 3·2 | –1·1 |
| **All patients** | 85% | 17% | 67% | 2·3 | 3·3 | –1·0 |

MI=myocardial infarction; 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%=–1·4 mmol/L for all patients; and, likewise, –1·2, –1·4, and –1·7 mmol/L, respectively, for those presenting with LDL cholesterol <3·0, ⩾3·0<3·5, and ⩾3·5 mmol/L.

Table 3: **Average use of statin (study or non-study), and average plasma LDL cholesterol concentrations, during follow-up**

| | Simvastatin-allocated (n=10 269) | Placebo-allocated (n=10 267) |
|---|---|---|
| **Elevated ALT** | | |
| 2–4×ULN | 139 (1·35%) | 131 (1·28%) |
| >4×ULN | 43 (0·42%) | 32 (0·31%) |
| **Elevated CK** | | |
| 4–10×ULN | 19 (0·19%) | 13 (0·13%) |
| >10×ULN* | 11 (0·11%) | 6 (0·06%) |
| **Myopathy** | | |
| No rhabdomyolysis | 5 (0·05%) | 1 (0·01%) |
| Rhabdomyolysis | 5 (0·05%) | 3 (0·03%) |

ALT=alanine aminotransferase; CK=creatine kinase; ULN=upper limit of normal for laboratory. *Among those with CK >10×ULN, 1 *vs* 2 were asymptomatic.

Table 4: **Numbers of participants with elevated liver or muscle enzymes during follow-up**

The proportional reduction in LDL cholesterol produced by actual use of 40 mg simvastatin daily is approximately independent of the presenting cholesterol concentration (see table 4 footnote). But, even for participants presenting with LDL cholesterol below 3 mmol/L (116 mg/dL), the average LDL cholesterol difference during the trial was 0·9 mmol/L (1·8 mmol/L [70 mg/dL] among those allocated simvastatin *vs* 2·7 mmol/L [104 mg/dL] among those allocated placebo). Hence, the intention-to-treat analyses of clinical outcomes should be informative in each of these subcategories.

*Effects on mortality*

During the scheduled treatment period, there were 1328 (12·9%) deaths among the 10 269 participants allocated 40 mg daily simvastatin compared with 1507 (14·7%) among the 10 267 allocated matching placebo (p=0·0003: figure 2). This effect of simvastatin allocation on all-cause mortality is due chiefly to the definite 17% (SE 4; 95% CI 9–25) proportional reduction in the death rate from vascular causes (781 [7·6%] simvastatin *vs* 937 [9·1%] placebo deaths; p<0·0001), which consists of a highly significant 18% (SE 5) reduction in the coronary death rate (587 [5·7%] *vs* 707 [6·9%]; p=0·0005) and a marginally significant 16% (SE 9) reduction in the death rate from other vascular causes (194 [1·9%] *vs* 230 [2·2%]; p=0·07). There were no significant differences either in all non-vascular deaths considered together (547 [5·3%] *vs* 570 [5·6%]; p=0·4) or in any of the prespecified categories of non-vascular deaths (for example, 10 *vs* 10 from renal causes, 5 *vs* 3 from hepatic causes, and 12 *vs* 16 from trauma, which includes 0 *vs* 1 from suicide).

*Effects on coronary and other vascular events*

*Coronary events*—In addition to the 18% (SE 5) reduction in the coronary mortality rate, allocation to simvastatin produced an even more extreme 38% (SE 5; 95% CI 30–46) proportional reduction in the incidence rate of first non-fatal myocardial infarction following randomisation (357 [3·5%] simvastatin *vs* 574 [5·6%] placebo; p<0·0001: figure 3). Combining these, there was a 27% (SE 4; 95% CI 21–33) proportional reduction in the incidence rate of non-fatal myocardial infarction or coronary death (ie, "major coronary events": 898 [8·7%] *vs* 1212 [11·8%]; p<0·0001). In addition, there was a significant reduction in the numbers of participants who, although not having such major coronary events during

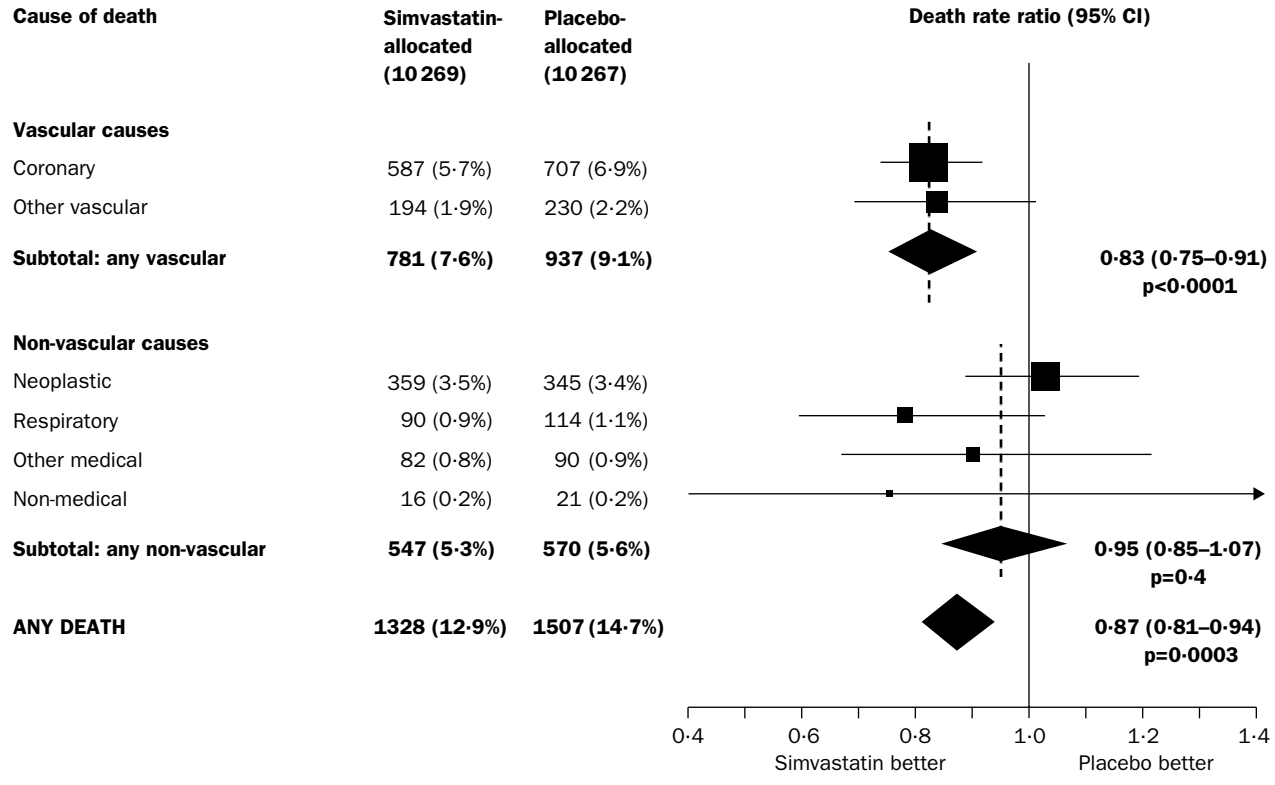



Figure 2: **Effects of simvastatin allocation on cause-specific mortality**

Rate ratios (RRs) are plotted (black squares with area proportional to the amount of statistical information in each subdivision) comparing outcome among participants allocated simvastatin to that among those allocated placebo, along with their 95% CIs (horizontal lines; ending with arrow head when CI extends beyond scale). For particular subtotals and totals, the result and its 95% CI are represented by a diamond, with the RR (95% CI) and its statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit with simvastatin, but this is conventionally significant (p<0·05) only if the horizontal line or diamond does not overlap the solid vertical line. A broken vertical line indicates the overall RR for a particular subtotal or total.

| Type of major vascular event | Simvastatin-allocated (10 269) | Placebo-allocated (10 267) | Event rate ratio (95% CI) |
|---|---|---|---|
| **Coronary events** | | | |
| Non-fatal MI | 357 (3·5%) | 574 (5·6%) | |
| Coronary death | 587 (5·7%) | 707 (6·9%) | |
| **Subtotal: major coronary event** | **898 (8·7%)** | **1212 (11·8%)** | **0·73 (0·67–0·79) p<0·0001** |
| **Strokes** | | | |
| Non-fatal stroke | 366 (3·6%) | 499 (4·9%) | |
| Fatal stroke | 96 (0·9%) | 119 (1·2%) | |
| **Subtotal: any stroke** | **444 (4·3%)** | **585 (5·7%)** | **0·75 (0·66–0·85) p<0·0001** |
| **Revascularisations** | | | |
| Coronary | 513 (5·0%) | 725 (7·1%) | |
| Non-coronary | 450 (4·4%) | 532 (5·2%) | |
| **Subtotal: any revascularisation** | **939 (9·1%)** | **1205 (11·7%)** | **0·76 (0·70–0·83) p<0·0001** |
| **ANY MAJOR VASCULAR EVENT** | **2033 (19·8%)** | **2585 (25·2%)** | **0·76 (0·72–0·81) p<0·0001** |

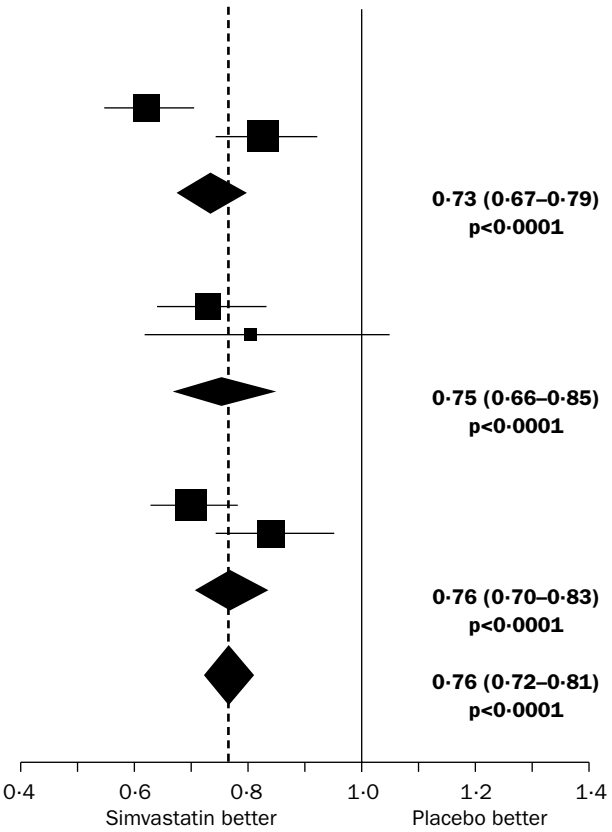



Figure 3: **Effects of simvastatin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as "major vascular events")**
Symbols and conventions as in figure 2. Analyses are of the numbers of participants having a first event of each type during follow-up (with non-fatal and fatal events also considered separately), so there is some non-additivity between different types of event. MI=myocardial infarction.

| Type and severity of stroke | Simvastatin-allocated (10 269) | Placebo-allocated (10 267) | Event rate ratio (95% CI) |
|---|---|---|---|
| **Type** | | | |
| Ischaemic | 290 (2·8%) | 409 (4·0%) | |
| Haemorrhagic | 51 (0·5%) | 53 (0·5%) | |
| Not classified | 103 (1·0%) | 134 (1·3%) | |
| **Severity** | | | |
| Fatal | 96 (0·9%) | 119 (1·2%) | |
| Severe | 42 (0·4%) | 51 (0·5%) | |
| Moderate | 107 (1·0%) | 155 (1·5%) | |
| Mild | 138 (1·3%) | 189 (1·8%) | |
| Not classified | 61 (0·6%) | 71 (0·7%) | |
| **ANY STROKE** | **444 (4·3%)** | **585 (5·7%)** | **0·75 (0·66–0·85) p<0·0001** |

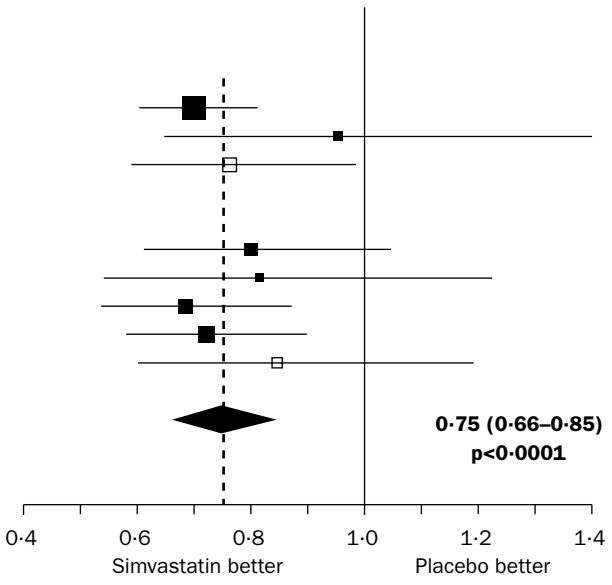



Figure 4: **Effects of simvastatin allocation on first stroke**
Symbols and conventions as in figure 2. For stroke type, analyses are of the numbers of participants having a first ischaemic or a first haemorrhagic stroke (with 11 having both stroke types), while those having only strokes that could not be classified are given in the final row. (Haemorrhagic stroke includes subarachnoid haemorrhage: 12 simvastatin-allocated *vs* 8 placebo-allocated.) For stroke severity, black squares relate to the most severe stroke that could be classified (so these categories are mutually exclusive). Open squares are used to indicate rate ratios for participants who had only strokes of unknown type or severity.

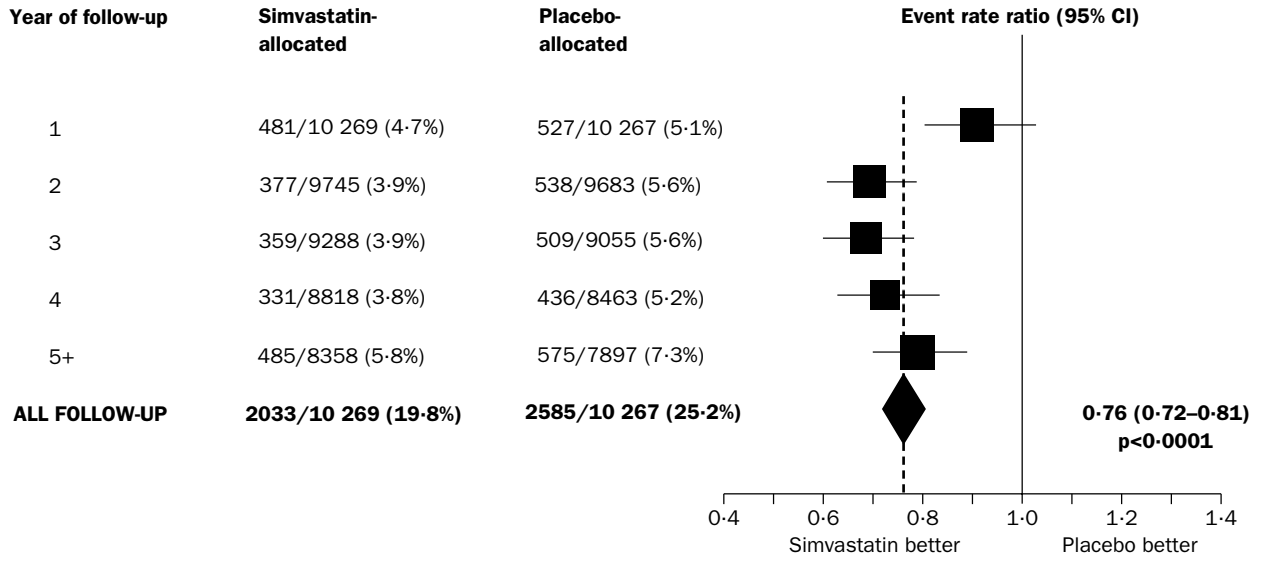



Figure 5: **Effects of simvastatin allocation on first major vascular event during follow-up**
Symbols and conventions as in figure 2. Analyses are of numbers of participants having a first event during each year of follow-up and of those still at risk of a first event at the start of each year.

follow-up, were admitted to hospital at least once for unstable or worsening angina (884 [8·6%] *vs* 1027 [10·0%]; p=0·0003).

*Stroke*—Overall, allocation to simvastatin produced a highly significant 25% (SE 5; 95% CI 15–34) proportional reduction in the incidence rate of first stroke following randomisation (444 [4·3%] simvastatin *vs* 585 [5·7%] placebo; p<0·0001: figure 3). This was due chiefly to a very definite 30% (SE 6; 95% CI 19–40) proportional reduction in the incidence rate of strokes attributed to ischaemia (290 [2·8%] *vs* 409 [4·0%]; p<0·0001), with no apparent difference in strokes attributed to haemorrhage (51 [0·5%] *vs* 53 [0·5%]; p=0·8: figure 4). Most strokes of known type were ischaemic, and there was a marginally significant (p=0·04) further reduction in the number of participants who only had a stroke of unknown type (most of which, presumably, were also ischaemic). Figure 4 also indicates about as great a reduction in fatal or severely disabling strokes as in less severe strokes (and would still do so even if the relatively few haemorrhagic strokes were excluded). In addition, there was a significant reduction in the numbers of participants who, although not having a stroke during follow-up, had at least one episode of transient cerebral ischaemia (204 [2·0%] *vs* 250 [2·4%]; p=0·02).

*Revascularisation*—Overall, allocation to simvastatin produced a highly significant 24% (SE 4; 95% CI 17–30) proportional reduction in the incidence rate of first revascularisation procedure following randomisation (939 [9·1%] simvastatin *vs* 1205 [11·7%] placebo; p<0·0001: figure 3). There were definite reductions in the numbers of participants undergoing coronary artery bypass surgery (324 [3·2%] *vs* 452 [4·4%]; p<0·0001) or coronary angioplasty (210 [2·0%] *vs* 305 [3·0%]; p<0·0001), which corresponds to a 30% (SE 5; 95% CI 22–38) proportional reduction in the incidence rate of coronary revascularisation (513 [5·0%] *vs* 725 [7·1%]; p<0·0001: figure 3). There was also a significant 16% (SE 6; 95% CI 5–26) proportional reduction in the incidence rate of non-coronary revascularisation (450 [4·4%] *vs* 532 [5·2%]; p=0·006). Half of that difference involved a definite reduction in carotid endarterectomy or angioplasty (42 [0·4%] *vs* 82 [0·8%]; p=0·0003).

*Effects on vascular events in different circumstances*
When these similar proportional reductions in major coronary events, in strokes, and in revascularisations are considered together, yielding analyses of the first occurrence of any of these "major vascular events", allocation to simvastatin was associated with a definite 24% (SE 3; 95% CI 19–28) proportional reduction in the event rate (2033 [19·8%] simvastatin *vs* 2585 [25·2%] placebo; p<0·0001: figure 3). The extreme statistical significance of this reduction (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. In this high-risk population, about 5% of placebo-allocated participants had a first major vascular event during each year of follow-up (figures 5 and 6). Among participants allocated simvastatin, there was already a non-significant trend (p=0·1) towards fewer major vascular events in the first year of follow-up after randomisation (figure 5). Subsequently, during each separate year of follow-up, there were highly significant reductions of about one-quarter in the event rates

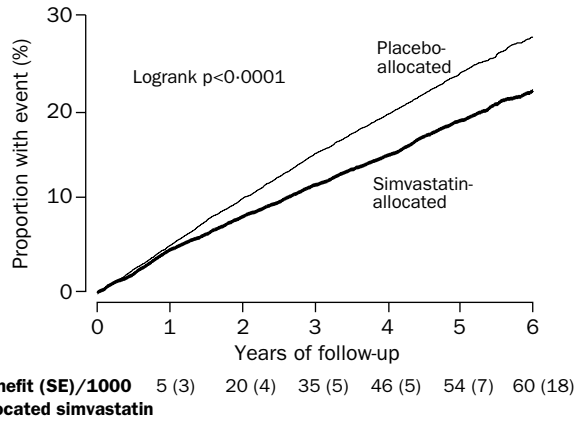
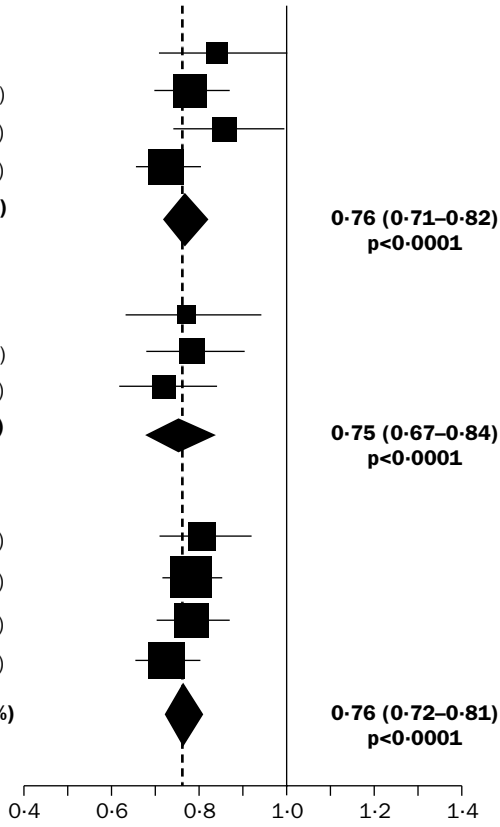



Figure 6: **Life-table plot of effects of simvastatin allocation on percentages having major vascular events**
See figure 5 for numbers of participants having a first event during each year of follow-up.

| Prior disease category | Simvastatin-allocated | Placebo-allocated |
|---|---|---|
| **Prior MI or other CHD** | | |
| + Cerebrovascular | 234/723 (32·4%) | 276/737 (37·4%) |
| + Peripheral vascular | 568/2059 (27·6%) | 681/1988 (34·3%) |
| + Diabetes mellitus | 325/972 (33·4%) | 381/1009 (37·8%) |
| + None of above | 617/3674 (16·8%) | 840/3740 (22·5%) |
| **Subtotal: any CHD** | **1459/6694 (21·8%)** | **1841/6692 (27·5%)** |
| **No prior CHD** | | |
| + Cerebrovascular | 172/922 (18·7%) | 212/898 (23·6%) |
| + Peripheral vascular | 327/1325 (24·7%) | 420/1376 (30·5%) |
| + Diabetes mellitus | 276/2006 (13·8%) | 367/1976 (18·6%) |
| **Subtotal: no CHD** | **574/3575 (16·1%)** | **744/3575 (20·8%)** |
| **CHD or no prior CHD** | | |
| + Cerebrovascular | 406/1645 (24·7%) | 488/1635 (29·8%) |
| + Peripheral vascular | 895/3384 (26·4%) | 1101/3364 (32·7%) |
| + Diabetes mellitus | 601/2978 (20·2%) | 748/2985 (25·1%) |
| + None of above | 628/3794 (16·6%) | 855/3858 (22·2%) |
| **ALL PATIENTS** | **2033/10 269 (19·8%)** | **2585/10 267 (25·2%)** |




Heterogeneity $\chi^2$ for "Any CHD" *vs* "No CHD"=0·1

Figure 7: **Effects of simvastatin allocation on first major vascular event in different prior disease categories**
Symbols and conventions as in figure 2. There is no overlap between participants in "Any CHD" and "No CHD" baseline disease categories, but within each of these categories there is some overlap (and, hence, some non-additivity). $\chi^2$ test on one degree of freedom is given for heterogeneity between rate ratios in participants with any prior coronary heart disease (CHD) versus those with no prior CHD.

(p<0·0001 in years 2–4; p=0·0002 in year 5+)—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 1). Indeed, one-third of the placebo-allocated participants were taking a statin by the end of year 5, and this would account for the slightly less extreme risk reductions shown in figure 5 during the last two years of the study.

The proportional reduction in the rate of major vascular events was about one-quarter in each subcategory of participants studied (figures 7 and 8; for major coronary events see http://image.thelancet.com/extras/02art5389webfigure1.pdf and http://image.the lancet.com/extras/02art5389webfigure2.pdf). In particular, there was a highly significant 25% (SE 5; 95% CI 16–33) proportional reduction (p<0·0001) among participants with no history of coronary disease at entry, with separately significant reductions observed among such individuals who had cerebrovascular disease (p=0·001), or had peripheral vascular disease (p<0·0001), or had diabetes (p<0·0001: figure 7). Most notably, the proportional reductions in risk did not appear to be materially influenced by the pretreatment cholesterol or triglyceride concentrations (figure 8). Thus, there were highly significant risk reductions among the 6793 participants whose pre-treatment measurements of LDL cholesterol were below 3·0 mmol/L (116 mg/dL: 598 [17·6%] simvastatin-allocated *vs* 756 [22·2%] placebo-allocated; p<0·0001) and, indeed, even among the 3421 presenting with LDL below 2·6 mmol/L (100 mg/dL: 282 [16·4%] *vs* 358 [21·0%]; p=0·0006). Similarly, there were highly significant risk reductions among the 4072 participants with pretreatment total cholesterol measurements below 5·0 mmol/L (193 mg/dL: 360 [17·7%] *vs* 472 [23·1%]; p<0·0001).

In randomised trials of statin therapy versus placebo, groups of patients defined by the size of their post-randomisation cholesterol reductions cannot be guaranteed—and, indeed, are unlikely—to differ only randomly from each other (since factors related to the apparent lipid response may well also be related to outcome). Hence, inferences drawn from comparisons of outcome between such groups[36–38] might be misleading.[32] By contrast in the present trial, the use by all participants of a few weeks of simvastatin during the pre-randomisation run-in period (see Methods) allows unbiased randomised comparisons of the effects of treatment on clinical outcomes within subgroups defined by each individual's apparent LDL cholesterol "responsiveness". Figure 8 shows that the apparent LDL response to simvastatin cannot be used to identify people who will obtain much greater, or much smaller, than average benefit. But, since the average LDL cholesterol differences during the study between those allocated simvastatin and those allocated placebo in these "LDL response" subgroups were quite similar (table 3), this

| Presenting feature | Simvastatin-allocated | Placebo-allocated | Heterogeneity or trend $\chi^2$ |
|---|---|---|---|
| **Prior disease** | | | |
| Prior MI | 999/4257(23·5%) | 1250/4253(29·4%) | 0·18 |
| Other CHD | 460/2437(18·9%) | 591/2439(24·2%) | |
| No prior CHD | 574/3575(16·1%) | 744/3575(20·8%) | |
| **Sex** | | | |
| Male | 1666/7727(21·6%) | 2135/7727(27·6%) | 0·76 |
| Female | 367/2542(14·4%) | 450/2540(17·7%) | |
| **Age (years)** | | | |
| <65 | 831/4903(16·9%) | 1091/4936(22·1%) | 0·73 |
| ⩾65 <70 | 512/2447(20·9%) | 665/2444(27·2%) | |
| ⩾70 | 690/2919(23·6%) | 829/2887(28·7%) | |
| **Total cholesterol (mmol/L)** | | | |
| <5·0 | 360/2030(17·7%) | 472/2042(23·1%) | 0·44 |
| ⩾5·0 <6·0 | 744/3942(18·9%) | 964/3941(24·5%) | |
| ⩾6·0 | 929/4297(21·6%) | 1149/4284(26·8%) | |
| **LDL cholesterol (mmol/L)** | | | |
| <3·0 | 598/3389(17·6%) | 756/3404(22·2%) | 0·10 |
| ⩾3·0 <3·5 | 484/2549(19·0%) | 646/2514(25·7%) | |
| ⩾3·5 | 951/4331(22·0%) | 1183/4349(27·2%) | |
| **HDL cholesterol (mmol/L)** | | | |
| <0·9 | 818/3617(22·6%) | 1064/3559(29·9%) | 1·98 |
| ⩾0·9 <1·1 | 560/2795(20·0%) | 720/2871(25·1%) | |
| ⩾1·1 | 655/3857(17·0%) | 801/3837(20·9%) | |
| **Triglycerides (mmol/L)** | | | |
| <2·0 | 1101/6011(18·3%) | 1432/6034(23·7%) | 0·65 |
| ⩾2·0 <4·0 | 743/3445(21·6%) | 939/3443(27·3%) | |
| ⩾4·0 | 189/813(23·2%) | 214/790(27·1%) | |
| **Prerandomisation LDL response** | | | |
| Smaller (<38%) | 700/3516(19·9%) | 911/3558(25·6%) | 0·08 |
| Average | 649/3252(20·0%) | 822/3272(25·1%) | |
| Larger (⩾48%) | 684/3501(19·5%) | 852/3437(24·8%) | |
| **Creatinine** | | | |
| Normal | 1851/9623(19·2%) | 2317/9584(24·2%) | 2·25 |
| Slightly elevated* | 182/646(28·2%) | 268/683(39·2%) | |
| **Cigarette smoking** | | | |
| Never regular | 406/2594(15·7%) | 531/2580(20·6%) | 0·45 |
| Ex-cigarette | 1298/6229(20·8%) | 1638/6220(26·3%) | |
| Current | 329/1446(22·8%) | 416/1467(28·4%) | |
| **Treated hypertension** | | | |
| Yes | 942/4211(22·4%) | 1195/4246(28·1%) | 0·00 |
| No | 1091/6058(18·0%) | 1390/6021(23·1%) | |
| **Aspirin** | | | |
| Yes | 1370/6482(21·1%) | 1784/6502(27·4%) | 1·35 |
| No | 663/3787(17·5%) | 801/3765(21·3%) | |
| **β-blockers** | | | |
| Yes | 519/2661(19·5%) | 705/2618(26·9%) | 3·27 |
| No | 1514/7608(19·9%) | 1880/7649(24·6%) | |
| **ACE inhibitors** | | | |
| Yes | 495/1989(24·9%) | 568/1990(28·5%) | 3·75 |
| No | 1538/8280(18·6%) | 2017/8277(24·4%) | |
| **Vitamin allocation** | | | |
| Vitamins | 1014/5135(19·7%) | 1292/5134(25·2%) | 0·03 |
| Placebo | 1019/5134(19·8%) | 1293/5133(25·2%) | |
| **ALL PATIENTS** | **2033/10 269(19·8%)** | **2585/10 267(25·2%)** | **0·76 (0·72–0·81) p<0·0001** |

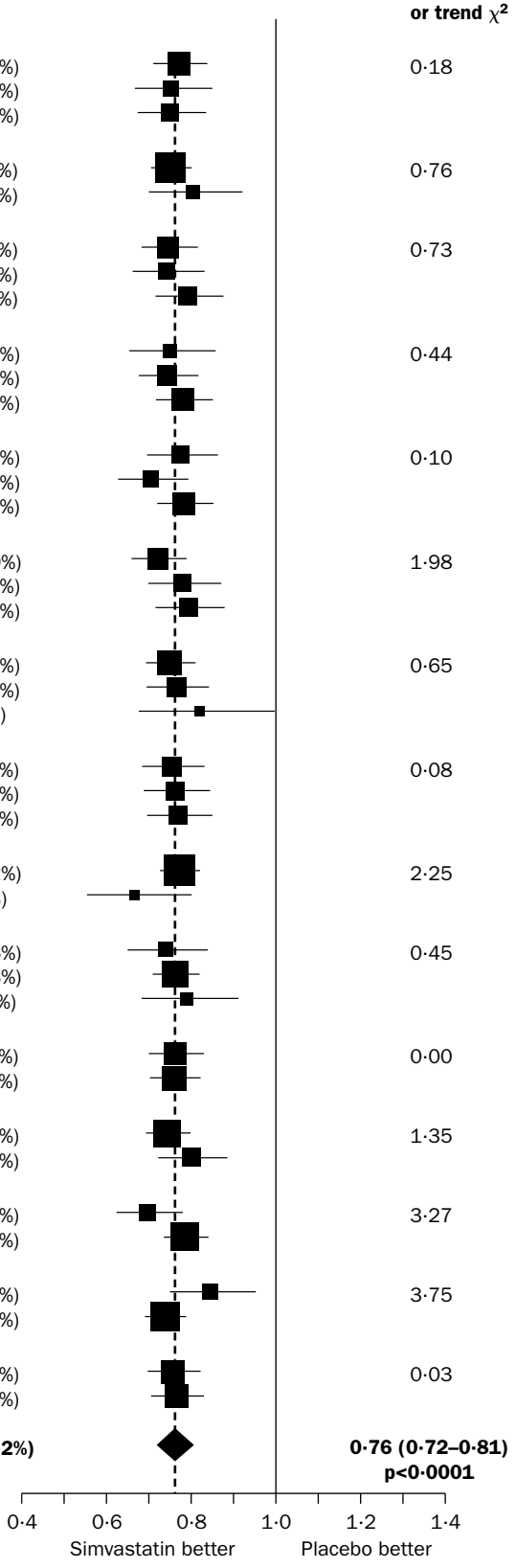



Figure 8: **Effects of simvastatin allocation on first major vascular event in different categories of participant**

Symbols and conventions as in figure 2. $\chi^2$ tests on one degree of freedom are given for heterogeneity between rate ratios within dichotomous categories and for trend within other categories (with value >3·84 equivalent to p<0·05 before making allowance for multiple comparisons). Lipid categories relate to measured values at the initial screening visit prior to starting any statin therapy. Prerandomisation "LDL response" relates to percent reduction in measured LDL cholesterol between the screening and randomisation clinic visits following 4–6 weeks of 40 mg simvastatin daily "run-in" treatment, which was provided to all patients (irrespective of their subsequent random allocation). Treatment for hypertension and other treatments recorded at entry to the study generally continued during follow-up (as did the vitamins allocated in the 2×2 factorial design[24]). *Slightly elevated creatinine defined as ⩾110 μmol/L for women and ⩾130 μmol/L for men, but <200 μmol/L for both.

indirect randomised comparison does not have good power to assess whether substantially larger reductions in LDL cholesterol do produce substantially larger reductions in risk.

The proportional reduction in the rate of major vascular events with allocation to simvastatin also seemed to be about one-quarter irrespective of the sex or the age of the participants. Indeed, even among the 1263 individuals aged 75–80 years at entry, and so aged about 80–85 years by the end of the study, the reduction in the event rate was substantial and definite (142 [23·1%] *vs* 209 [32·3%]; p=0·0002). In addition, the proportional risk reduction appeared to be largely independent of the blood creatinine concentration at entry (although only a few hundred participants had concentrations of 150–200 μmol/L, with none above 200 μmol/L), of cigarette smoking, of treatment for hypertension, and of the use of aspirin, β-blockers, and angiotensin-converting-enzyme inhibitors (figure 8). Although these analyses relate only to the use of those other treatments at entry to the study, such use generally continued throughout the study. Hence, the benefits of adding simvastatin are additional to the benefits of these other cardioprotective treatments. There was no suggestion that the proportional reductions in major vascular events were different among participants who had, or had not, been allocated the study vitamins (which, as discussed in the accompanying article,[24] did not produce any significant benefits or hazards).

*Effects on cancer incidence*

New primary cancers (excluding non-melanoma skin cancer) were diagnosed in 814 (7·9%) of the participants allocated simvastatin compared with 803 (7·8%) of those allocated placebo (rate ratio [RR] 1·00; 95% CI 0·91–1·11: figure 9), and were associated with death in 359 (3·5%) versus 345 (3·4%) participants (RR 1·03; 95% CI 0·89–1·19: figure 2). These differences were not significant, and nor were there significant differences between the treatment groups in the incidence of cancers in any particular body system (figure 9). An apparent excess was observed in simvastatin-allocated participants diagnosed with non-melanoma skin cancer during follow-up (243 [2·4%] *vs* 202 [2·0%]; only one of which was fatal), but this difference was not conventionally significant (p=0·06) even before allowing for the multiple comparisons involved. When cancer sites were more finely divided to investigate specific hypotheses raised by previous studies, there were still no significant differences between the treatment groups (for example, breast cancer: 38 [1·5%] simvastatin-allocated *vs* 51 [2·0%] placebo-allocated women; p=0·2).

*Effects on liver and muscle enzymes*

*Liver enzymes*—Blood concentrations of alanine aminotransferase were to be measured at each follow-up visit, even if participants no longer continued their study treatment. Despite the large numbers tested, few were ever found to have elevated alanine aminotransferase concentrations, and there was no significant excess among those allocated simvastatin (table 4). In such cases, study treatment was generally continued and another blood sample collected within 3 weeks, with persistent elevations found only rarely (>4×ULN: 9 [0·09%] simvastatin *vs* 4 [0·04%] placebo; p=0·3). Moreover, there was no significant difference between the groups in the numbers of participants whose study treatment was stopped because of elevated liver enzymes (48 [0·5%] *vs* 35 [0·3%]).

*Muscle enzymes and myopathy*—At each of the scheduled follow-up visits, about 6% of the participants reported unexplained muscle pain or weakness, but at no stage was there any significant difference between the treatment groups (with such symptoms reported on at least one occasion by 32·9% simvastatin-allocated *vs* 33·2% placebo-allocated participants). Nor was there any significant difference between the groups in the numbers of participants whose study treatment was stopped because of muscle symptoms (49 [0·5%] *vs* 50 [0·5%]). Creatine kinase was to be measured in any participant reporting such symptoms, as well as in those who continued their study simvastatin/placebo tablets after starting non-study statin therapy (and, on some occasions,

| Cancer site (primary) | Simvastatin-allocated (10 269) | Placebo-allocated (10 267) |
|---|---|---|
| Gastrointestinal | 228 (2·2%) | 223 (2·2%) |
| Respiratory | 179 (1·7%) | 167 (1·6%) |
| Connective tissue* | 60 (0·6%) | 68 (0·7%) |
| Genitourinary | 259 (2·5%) | 272 (2·6%) |
| Central nervous system | 12 (0·1%) | 7 (0·1%) |
| Haematological | 64 (0·6%) | 52 (0·5%) |
| Other | 6 (0·1%) | 2 (0·0%) |
| Not specified | 36 (0·4%) | 49 (0·5%) |
| **ANY CANCER (except non-melanoma skin)** | **814 (7·9%)** | **803 (7·8%)** |
| Non-melanoma skin | 243 (2·4%) | 202 (2·0%) |

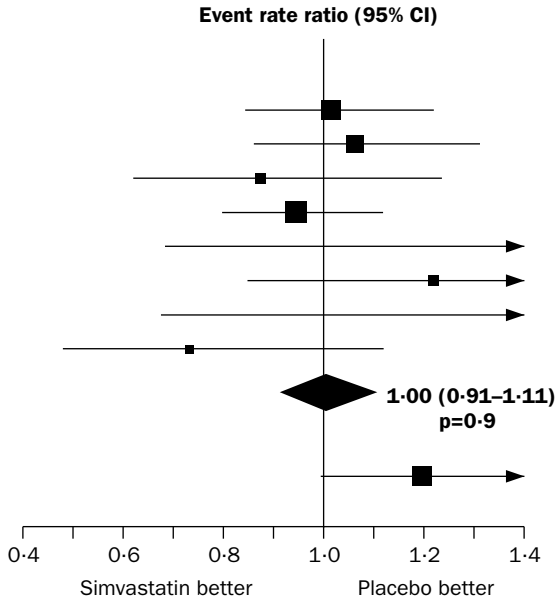



Figure 9: **Effects of simvastatin allocation on site-specific cancer incidence**
Symbols and conventions as in figure 2. Analyses are of the numbers of participants developing cancer at each site (excluding recurrences or new cancers at the same site), so there is some non-additivity between cancers at different sites. *Not including non-melanoma skin cancer, which is given separately.

was reported directly by the participant's own doctor). Few of the participants were ever found to have elevated creatine kinase concentrations (table 4). Only a slight, and non-significant (p=0·2), excess of simvastatin-allocated participants was diagnosed to have myopathy, which was defined as muscle symptoms plus creatine kinase above 10×ULN (although one case in the placebo group was taking a non-study statin). Some of these myopathy cases developed rhabdomyolysis (creatine kinase >40×ULN), but none was fatal. Study treatment was to be stopped immediately when myopathy was identified, but it was generally continued with less marked creatine kinase elevations and another blood sample collected within about 1 week. Persistent elevations were found rarely in those participants (>4×ULN: 7 [0·07%] *vs* 1 [0·01%]; p=0·07) and only one in each treatment group progressed to myopathy.

### *Effects on other outcomes*

*Neuropsychiatric disorders*—It had been reported from observational studies that lowering cholesterol with statins might slow cognitive decline, perhaps through reductions in cerebrovascular atherosclerosis.[39–41] The well validated modified Telephone Interview for Cognitive Status (TICS-m) questionnaire[42] was, therefore, administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. 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 among those with a previous stroke (see below). But, despite this discriminatory ability, no significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired, either overall (23·7% simvastatin-allocated *vs* 24·2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17·1% *vs* 17·8%; 65–69 years: 25·8% *vs* 25·4%; 70–80 years: 34·6% *vs* 36·2%) or their previous history of cerebrovascular disease (no prior stroke: 22·8% *vs* 23·3%; prior stroke: 31·9% *vs* 33·3%). Nor was there any significant difference between the groups in mean TICS-m score (24·08 *vs* 24·06; difference 0·02 [SE 0·07]). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0·3%] *vs* 31 [0·3%]), to have some other psychiatric disorder (67 [0·7%] *vs* 60 [0·6%]), or to have attempted suicide (14 [0·1%] *vs* 11 [0·1%]).

*Respiratory disease*—Low cholesterol has been associated in observational studies with increased mortality from chronic obstructive pulmonary disease,[1] so respiratory function was assessed by spirometry in all those attending the final follow-up visit. No significant differences were observed between the treatment groups in forced expiratory volume during one second ($FEV_1$: 2·06 L simvastatin-allocated *vs* 2·05 L placebo-allocated; difference 0·01 L [SE 0·01]) or in forced vital capacity (FVC: 2·82 L *vs* 2·82 L; difference 0·00 L [SE 0·01]). Nor were significant differences observed in the numbers of participants hospitalised for chronic obstructive pulmonary disease or asthma (132 [1·3%] *vs* 150 [1·5%]) or for any other non-neoplastic respiratory cause (633 [6·2%] *vs* 650 [6·3%]).

*Fractures*—Based on non-randomised observational study findings, it had been suggested that statins might prevent osteoporosis and fractures.[43,44] Tertiary comparisons were, therefore, prespecified of the effects of the allocated simvastatin on hospitalisation for fracture (excluding the few related to road-traffic accidents). No significant differences were observed in the numbers of participants having any such fracture (241 [2·3%] simvastatin *vs* 230 [2·2%] placebo) or those that are particularly related to osteoporosis (ie, hip, wrist, or spine: 109 [1·1%] *vs* 91 [0·9%]). These results are consistent with the recent report from the randomised Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial.[45]

*Other outcomes*—There did not appear to be any significant difference between the treatment groups in the numbers hospitalised for any other particular reason (even before making allowance for the exploratory nature of such analyses). In addition, discontinuation of allocated treatment was attributed to adverse events for similar numbers of participants in the two groups (4·8% simvastatin-allocated *vs* 5·1% placebo-allocated). No significant differences were observed between the treatment groups in blood pressure or bodyweight recorded at the final follow-up visit.

## Discussion

### *Benefits for a wide range of high-risk patients*

The results of the Heart Protection Study demonstrate that lowering LDL cholesterol with a statin produces a substantial reduction in the incidence of major vascular events among a much wider range of high-risk individuals than had previously been shown to benefit from such treatment. In particular, it demonstrates substantial benefit not only in those already known to have coronary disease, but also in those without diagnosed coronary disease who have cerebrovascular disease, or peripheral arterial disease, or diabetes (for each of which there had previously been little direct evidence of benefit), irrespective of the blood lipid concentrations when treatment is initiated. The large numbers of participants studied in a wide range of different circumstances (eg, prior disease, age, sex, presenting lipid concentrations, other management) allow these results to be generalised widely.[32] Moreover, since high-risk individuals with diagnosed occlusive arterial disease or diabetes have—by definition—already been identified, widespread implementation of these findings would be comparatively straightforward, without the need for extensive screening of the general population.

Previous randomised trials of cholesterol-lowering therapy tended to include people with pre-existing heart disease and to exclude older individuals, so they chiefly involved middle-aged men (since women tend to develop heart disease at an older age than men do).[6–11] The present study deliberately included large numbers of older individuals and of women, and it demonstrates substantial benefit in old age as well as middle age, and in women as well as men. The antioxidant vitamins that were also studied did not influence the effects of simvastatin on blood lipids or on vascular disease outcomes. Indeed, the benefits of statin therapy appeared to be largely independent of, and hence additional to, those of all the other treatments being used by the participants, including antihypertensive therapy and various other types of cardioprotective drug (eg, aspirin, β-blockers, and angiotensin-converting-enzyme inhibitors: figure 8).

Much larger numbers of participants suffered a stroke in the Heart Protection Study than in any previous cholesterol-lowering trial,[6–11,46] resolving any remaining uncertainties about the effects of statin therapy on the incidence of stroke.[47] There was a definite and substantial reduction in ischaemic stroke, with an additional reduction in transient cerebral ischaemic attacks. Similar numbers of participants in the two treatment groups

suffered a haemorrhagic stroke, which provides some refutation of previous concerns that lowering cholesterol might increase the risk of cerebral haemorrhage.[1] Cholesterol-lowering therapy had previously been shown to reduce the need for coronary artery revascularisation procedures,[6,48] and the present study extends this evidence of benefit to carotid endarterectomy and other peripheral artery revascularisations (as well as confirming the reduction in hospitalisation for worsening angina seen in the LIPID trial[10]). In addition, the much larger numbers of participants in the Heart Protection Study who developed cancers or died from non-vascular causes than in any previous trial provide considerable reassurance about the 5-year safety of lowering LDL cholesterol substantially (even among people who present with relatively low levels). So, for example, the observation in the Cholesterol And Recurrent Events (CARE) randomised trial of breast cancer in 12 women allocated pravastatin compared with only one allocated placebo[8] is not supported by the much larger numbers of women who developed breast cancer in the present study or in the other main statin trials.[6,7,9–11] Participants will, however, continue to be followed up for several years to determine whether, after an average of 5 years of a substantial cholesterol reduction with statin therapy, any delayed effects on cancers or other major outcomes emerge.

Statin therapy has been associated with an increased incidence of muscle pain and weakness (particularly when used at high doses or in combination with certain other drugs), and cerivastatin was recently withdrawn because of unacceptably high rates of myopathy and rhabdomyolysis.[49] In the present study, however, there was no difference between the treatment groups in reports of muscle symptoms, and the annual excess risk of myopathy with 40 mg simvastatin daily was only about 0·01%. Following initiation of this regimen, therefore, it would seem to be sufficient to check creatine kinase concentrations only when definite unexplained muscle symptoms are reported (unless patients are also using other drugs known to increase the risk of myopathy). Similarly, the present findings suggest that there is no need for routine liver function checks when using this regimen or other statin regimens with similar safety data from large-scale randomised trials[6–11] (except, perhaps, to identify and then monitor people with pre-existing liver disease).

### *Lack of evidence for LDL cholesterol threshold*

It had been suggested that there might be a threshold of LDL cholesterol at about 3·2 mmol/L (125 mg/dL), below which lowering it would not reduce risk.[8,48] By contrast, the present study has demonstrated unequivocally that lowering LDL cholesterol from below 3 mmol/L to below 2 mmol/L (ie, below 116 to below 77 mg/dL) reduces vascular disease risk by about one-quarter, which is similar to the proportional reduction in risk produced by a 1 mmol/L reduction at higher LDL cholesterol concentrations. The Adult Treatment Panel (ATP III) of the US National Cholesterol Education Program has recently recommended that the LDL cholesterol concentrations of people considered to be at high risk because of pre-existing coronary disease (or at equivalent coronary risk for other reasons) be reduced to below 2·6 mmol/L (100 mg/dL).[50] In the Heart Protection Study, about 3500 participants presented with a pretreatment LDL cholesterol measurement that was already below this "target" level. Even among them, reducing the average LDL cholesterol during the trial from 2·5 mmol/L (97 mg/dL) in those allocated placebo to 1·7 mmol/L (65 mg/dL) in those allocated simvastatin was safe, and produced a reduction in risk about as great as that seen among those presenting with higher LDL cholesterol concentrations. 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. They also indicate that current guidelines may inadvertently lead to substantial under-treatment of high-risk patients who present with LDL cholesterol concentrations below, or close to, particular targets (such as 2·6 mmol/L [100 mg/dL] in the ATP III guidelines,[50] or 3·0 mmol/L [116 mg/dL] in the Second European Joint Task Force recommendations[51]).

The present results indicate that, within just a few years of lowering LDL cholesterol, vascular disease risk is reduced by about half as much as would be expected epidemiologically from a long-term difference of the same magnitude.[2,4] They also suggest that more prolonged reductions in LDL cholesterol with statin therapy would eventually produce even larger reductions in risk. In this trial, a 1 mmol/L reduction in LDL cholesterol from about 4 mmol/L to 3 mmol/L reduced the risk of major vascular events by about one-quarter, and so too did reducing it from about 3 mmol/L to 2 mmol/L (as might be expected from the approximately loglinear association in observational studies between vascular disease rates and usual LDL cholesterol concentrations[2,4]). This result provides indirect evidence that larger reductions in LDL cholesterol would produce larger risk reductions, which is currently the subject of large directly randomised comparisons.[14] Moreover, these findings suggest that, other things being equal, a downward shift of the whole LDL cholesterol distribution typically found in Western populations would lead to reductions in the incidence of vascular disease (and there was no evidence in the present trial that such a change would be associated with any material adverse effects).

### *More appropriate "high-risk" treatment strategy*

Many of the current guidelines base recommendations about the initiation of cholesterol-lowering therapy on a person's estimated risk of suffering just coronary events (eg, 10-year rates of at least 20% in ATP III[50]). The Heart Protection Study has, however, shown unequivocally that statin therapy prevents not just coronary events and coronary revascularisations, but also ischaemic strokes and peripheral revascularisations. Hence, decisions about whether to initiate therapy should perhaps now be guided by the estimated risk of suffering any such major vascular event, and not just a coronary event. In the present study, the chief determinant of absolute risk was the type of pre-existing disease (ie, coronary disease, other occlusive arterial disease, diabetes, or some combination of these conditions), with 5-year risks of major vascular events in the placebo group that ranged from about 20% to about 30% (figure 7; corresponding to 10-year risks of over 40%). Among the high-risk individuals in the various different categories considered, statin therapy produced substantial benefits that were not much influenced by the initial concentrations of blood lipids. Indeed, the results suggest that it might be worth considering statin therapy in people at somewhat lower risk of these major vascular events than those in the present study. For example, patients considered to be at sufficient risk of stroke and heart attack for antihypertensive therapy to be indicated

(particularly those who are older and have complicated hypertension) may well obtain substantial additional benefit from the addition of statin therapy. The clear demonstration of a reduction in ischaemic stroke, without any evidence of an adverse effect on haemorrhagic stroke, also suggests that statin therapy could 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 disease risk are relatively low.[3,52]

### Conclusions

Lowering cholesterol with 40 mg simvastatin daily produces substantial reductions in the rates of major vascular events among a wide range of high-risk individuals irrespective of their initial cholesterol concentrations, and these benefits are additional to those of other treatments (such as aspirin, β-blockers, angiotensin-converting-enzyme inhibitors, and other antihypertensive therapy[53–56]) that have also been shown to be beneficial for such people. During the study, an average of about one-sixth of the participants allocated 40 mg simvastatin daily stopped taking statin therapy, and about one-sixth of those allocated placebo started to take a statin. As a consequence, the average difference in LDL cholesterol of about 1 mmol/L that was observed between all those allocated simvastatin and all those allocated placebo represents only about two-thirds of the LDL-difference produced by actual use of 40 mg simvastatin daily. Similarly, the reduction of about one-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 in this population and would probably reduce the rates of heart attacks, strokes, and revascularisations by about one-third. Consequently, among the types of high-risk individuals studied (with 5-year placebo-group event rates of about 20–30%), treatment for 5 years should prevent about 70–100 people per 1000 from suffering at least one of these major vascular events, largely irrespective of age, sex, or presenting cholesterol concentrations (and more prolonged treatment should eventually produce even bigger absolute benefits). Moreover, since simvastatin not only reduced the risk of a first event being suffered by a person but also reduced the risk of subsequent events (which will be the subject of a future report), the numbers of major vascular events prevented per 1000 people treated for 5 years would be even larger. It seems likely, therefore, that such treatment will be considered worthwhile for many types of high-risk patients who are not currently being treated, particularly since it has been shown to be so well tolerated and safe.

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### *Conflict of interest statement*

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