From the Society for Vascular Surgery

Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions

Heart Protection Study Collaborative Group[1]

Objectives: **The Heart Protection Study (HPS) provides an opportunity to assess directly the effects of cholesterol-lowering therapy on major vascular events (defined as myocardial infarction, coronary death, stroke, or revascularization) in patients with peripheral arterial disease (PAD). In addition, the effects on peripheral vascular events (ie, non-coronary revascularization, aneurysm repairs, major amputations or PAD deaths) can be assessed.**

Methods: **6748 UK adults with PAD and 13,788 other high-risk participants were randomly allocated to receive 40 mg simvastatin daily or matching placebo, yielding an average LDL cholesterol difference of 1.0 mmol/L (39 mg/dL) during a mean of 5 years.**

Results: **For participants with PAD, allocation to simvastatin was associated with a highly significant 22% (95% CI 15-29) relative reduction in the rate of first major vascular event following randomisation (895 [26.4%] simvastatin-allocated vs 1101 [32.7%] placebo-allocated; $P < .0001$), which was similar to that seen among the other high-risk participants. The absolute reduction in first major vascular event was 63 (SE 11) per 1000 patients with PAD and 50 (SE 7) per 1000 without pre-existing PAD. Overall, among all participants, there was a 16% (5-25) relative reduction in the rate of first peripheral vascular event following randomisation (479 [4.7%] simvastatin vs 561 [5.5%] placebo), largely irrespective of baseline LDL cholesterol and other factors. This effect chiefly reflects a 20% (8-31) relative reduction in non-coronary revascularization procedures (334 [3.3%] vs 415 [4.0%]; $P = .002$).**

Conclusion: **HPS demonstrates the benefits of cholesterol-lowering statin therapy in patients with PAD, regardless of their presenting cholesterol levels and other presenting features. Allocation to 40 mg simvastatin daily reduces the rate of first major vascular events by about one-quarter, and that of peripheral vascular events by about one-sixth, with large absolute benefits seen in participants with PAD because of their high vascular risk. Consequently, statin therapy should be considered routinely for all patients with PAD. (J Vasc Surg 2007;45:645-54.)**

Peripheral arterial disease (PAD) is a common condition, with a prevalence of up to 20% in populations aged over 65 years.[1-3] It is associated with a marked increase in cardiovascular risk in patients both with and without co-existing coronary artery disease.[4] Observational studies in different populations indicate a continuous, positive and log-linear relationship between coronary disease risk and blood cholesterol concentration that extends well below the range commonly seen in Western populations, without any definite threshold below which a lower concentration is not associated with lower risk.[5-8] The risk factors for coronary and peripheral arterial disease are similar, and higher cholesterol concentrations are associated with higher rates of peripheral arterial disease.[9]

Despite the high incidence of cardiovascular morbidity and mortality in patients with PAD, relatively few such patients had been included in previous randomized controlled trials of cholesterol-lowering statin therapy.[10-15] By

[1]Writing and other Committees are listed in the Appendix, and collaborators and participating hospitals are listed in reference 17.

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Competition of interest: 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. Members of the writing committee have, therefore, only had such costs reimbursed.

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Correspondence to: Heart Protection Study, Clinical Trial Service Unit and Epidemiological Studies Unit, Richard Doll Building, University of Oxford, Old Road Campus, Roosevelt Dr, Oxford OX3 7LF, UK (e-mail: hps@ctsu.ox.ac.uk).

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contrast, the MRC/BHF Heart Protection Study (HPS) has demonstrated that lowering LDL cholesterol concentrations with 40 mg simvastatin daily produces substantial reductions in the rates of heart attacks, strokes, and revascularization procedures among a wide range of high-risk individuals, including the large numbers with PAD.[16-19] Despite this clear evidence of benefit, almost two-thirds of patients with PAD are still not receiving statin therapy.[20] The aim of the present report is to provide more details from HPS about the benefits of cholesterol-lowering with statin therapy in patients with PAD.

PATIENTS AND METHODS

Details of the study have been reported previously[16-19] (see also www.hpsinfo.org). In brief, 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 coronary disease, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and aged at least 65 years). PAD was defined as a history of intermittent claudication (with or without supporting vascular investigations) or previous peripheral arterial revascularization procedure, amputation, or aneurysm repair. People were ineligible if their own doctor considered statin therapy to be clearly indicated or contraindicated, or if they had myocardial infarction, stroke or hospital admission for angina within the previous 6 months; chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of substantially impaired renal function; inflammatory muscle disease or evidence of muscle problems; concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential; severe heart failure; or other conditions that might limit long-term compliance.

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).[21] These logrank analyses yielded both the event rate ratio and the test of statistical significance (two-sided probability value). Assessments of the effects of treatment in different prespecified subcategories of prior disease (including PAD) and of other presenting features were to be based on first major coronary events (defined as non-fatal myocardial infarction or death from coronary disease), and, particularly, on the even larger number of first major vascular events (defined as major coronary events, strokes of any type, and coronary or non-coronary revascularizations). Tests for heterogeneity or, if more appropriate, trend were to be used to determine whether the proportional effects observed in specific subcategories differed clearly from the overall effects (after due allowance for multiple comparisons and the exploratory nature of some analyses). Subsidiary comparisons included assessment of the effects of allocation to simvastatin not just on the rate of first major vascular events following randomisation, but also on the numbers of first and subsequent events during the scheduled treatment period, and of the effects on non-coronary vascular procedures (ie, carotid endarterectomy or angioplasty, other arterial grafts or angioplasty, and amputation). For the purposes of the present report, exploratory analyses were performed assessing the effects of statin allocation on peripheral vascular events (defined retrospectively as the first occurrence of a non-coronary revascularization, aneurysm repair, major amputation, or death from PAD).

Table I. Baseline characteristics of participants presenting with or without peripheral artery disease (PAD)

Baseline Feature	*Peripheral artery disease (n = 6748)*	*No peripheral artery disease (n = 13788)*
Age (years)	64.5 (8.1)	63.7 (8.5)
Men	5014 (74%)	10440 (76%)
Smoking		
Never regular	1093 (16%)	4081 (30%)
Ex-cigarette	4258 (63%)	8191 (59%)
Current	1397 (21%)	1516 (11%)
Vascular disease		
Prior MI	2372 (35%)	6138 (45%)
Other CHD	1675 (25%)	3201 (23%)
Cerebrovascular	521 (8%)	1299 (9%)
Diabetes	1579 (23%)	4384 (32%)
Treated hypertension	2898 (43%)	5559 (40%)
Systolic BP (mmHg)	146 (24)	143 (23)
Diastolic BP (mmHg)	81 (13)	82 (12)
Body mass index (kg/m^2)	27.6 (4.4)	27.6 (4.4)
Total cholesterol (mmol/L)	6.0 (1.05)	5.8 (0.99)
LDL cholesterol (mmol/L)	3.5 (0.86)	3.3 (0.80)
HDL cholesterol (mmol/L)	1.04 (0.32)	1.07 (0.33)
Triglycerides (mmol/L)	2.2 (1.42)	2.0 (1.34)
Apolipoprotein A_1 (mg/dL)	1.19 (0.22)	1.20 (0.22)
Apolipoprotein B (mg/dL)	1.17 (0.24)	1.13 (0.23)

MI, Myocardial infarction; *CHD,* coronary heart disease; *BP,* blood pressure; LDL, low-density lipoprotein; *HDL,* high-density lipoprotein.
Values are mean (and standard deviation) or number of participants (and percentage).

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

RESULTS

Between July 1994 and May 1997, 6748 people aged 40-80 years with PAD and a further 13,788 high-risk patients without diagnosed PAD were randomly allocated to receive 40 mg simvastatin daily or matching placebo tablets in a double-blind manner (and, separately, using a two-by-two factorial design, antioxidant vitamins or matching placebo capsules[22]). Among participants presenting with a history of PAD, 33% had undergone peripheral arterial surgery or angioplasty and 2% had had an amputation, while the remainder had symptomatic PAD. Of the trial participants with PAD, 60% had coronary heart disease (CHD), 8% had cerebrovascular disease, and 23% had

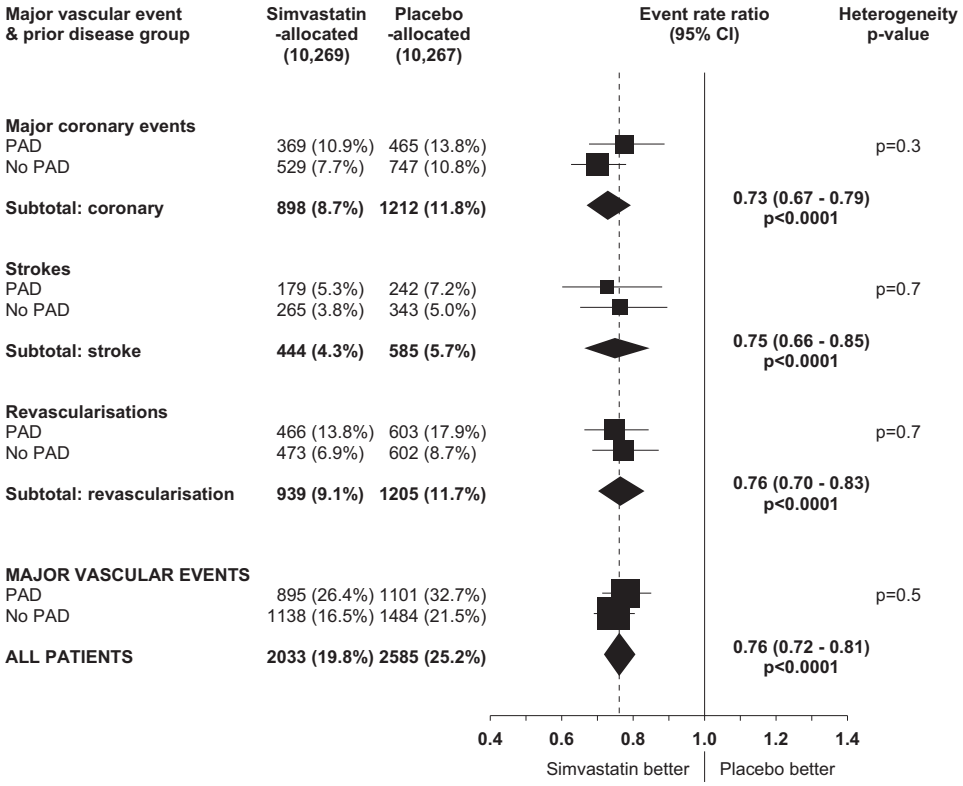

Fig 1. Effects of simvastatin allocation on first major coronary event, stroke, or revascularization in participants presenting with or without peripheral artery disease. Rate ratios (RRs) are plotted (*black squares* with area proportional to the amount of statistical information in each subdivision) comparing outcome among participants allocated simvastatin to that among those allocated placebo, along with their 95% CIs *(horizontal lines)*. 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 ($P < .05$) 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. *P*-values without adjustment for multiplicity are given for heterogeneity between rate ratios. Analyses are of the number of participants with a first event of each type during follow-up, so there is some non-additivity between different types of events.

diabetes (Table I). Compared with participants without PAD, those who had PAD were more likely to be current or ex cigarette smokers (84% vs 70%) and had slightly higher mean total and LDL cholesterol and triglycerides. Diabetes was less common in the PAD subgroup, largely due to the selective enrolment of almost 3000 diabetic patients who did not have overt occlusive arterial disease. The large size of the study (and the use of minimized randomisation[23]) produced good balance between the treatment groups among participants within both the PAD and non-PAD groups for the main prognostic features that were measured (and should have done likewise for those that were not).

Compliance and effect on blood lipids. The mean duration of follow-up was 5.0 years for all randomized participants: 5.3 years for those who survived to the scheduled end of the study treatment and about half that for those who did not. 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 (based on questioning the participant and review of remaining calendar-packed tablets). Among all participants allocated 40 mg simvastatin daily, average statin use during the scheduled treatment period was 85% (with 82% compliant with their allocated simvastatin, 3% on non-study statin alone and 2% on both: Table II, online only). By contrast, amongst those allocated placebo, an average of 17% were taking non-study statin therapy during the study. This average absolute difference in statin use of 67% (85% minus 17%) between all participants allocated simvastatin and all those allocated placebo yielded an average difference in LDL cholesterol of 1.0 mmol/L (suggesting that actual use of 40 mg simvastatin would reduce LDL cholesterol by an average of about 1.5 mmol/L in this population). Non-study statin use in the placebo group was more common among those who already had diagnosed coronary disease at entry, were younger or had higher pre-treatment LDL cholesterol concentrations, but it was not influenced by the presence of PAD (Table II, online only). The

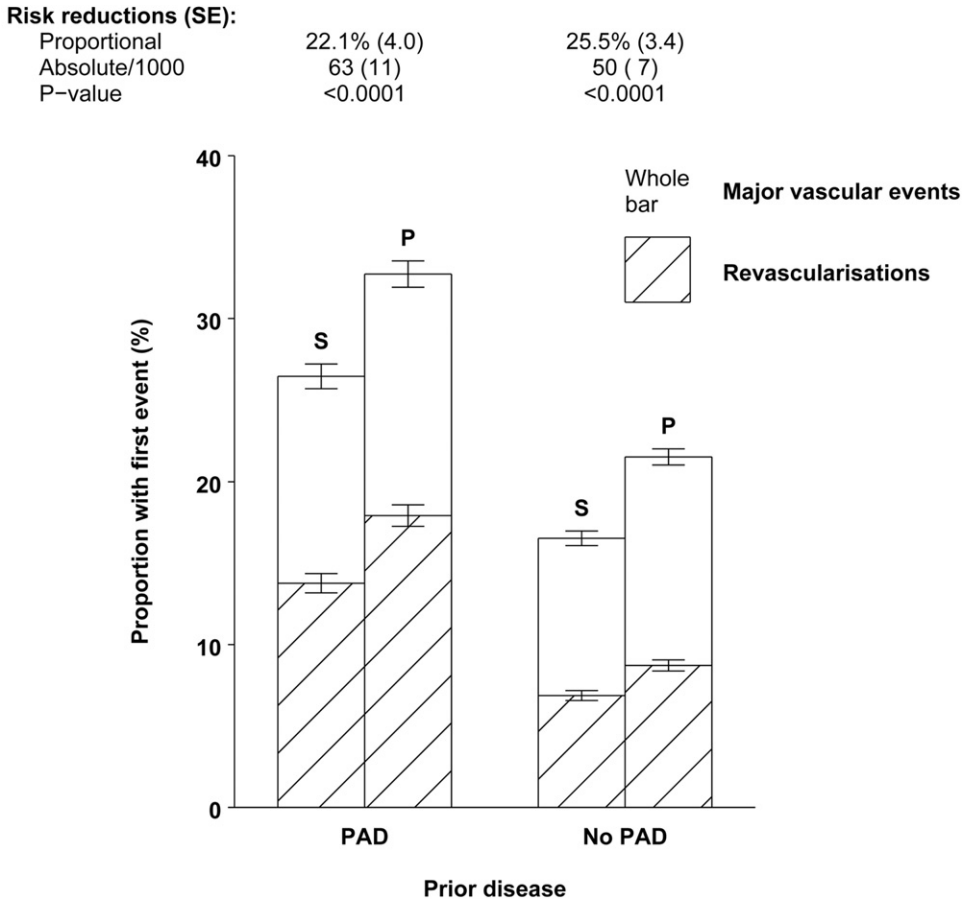

Fig 2. Absolute effects of simvastatin allocation on 5-year rates of first major vascular events among participants subdivided by prior PAD. *S,* Simvastatin allocated; *P,* placebo-allocated. Shaded portion of each bar represents percentage having a revascularization during follow-up.

average differences in plasma lipid concentrations during follow-up were similar in those with and without PAD at baseline.

Effects on major vascular events in the presence and absence of PAD. Overall, allocation to simvastatin produced a very highly significant 24% (95% CI 19-28; $P <$ .0001) proportional reduction in the first occurrence of a major vascular event following randomisation (Fig 1). Among the participants with diagnosed PAD at study entry there was a highly significant 22% (15-29; $P <$ .0001) proportional reduction in major vascular events, which was similar to the 25% (20-31; $P <$ .0001) reduction among the other high-risk participants studied (heterogeneity $P = .5$) Similar proportional reductions were also observed among patients with or without PAD in the rates of first major coronary event, stroke, and revascularizations considered separately (Fig 1). The 24% (17-30; $P <$ .0001) reduction in the rate of any revascularization procedure observed among all participants reflected a 30% (22-38; $P <$ .0001) reduction in coronary revascularizations and a 16% (5-26; $P = .006$) reduction in non-coronary revascularizations (including amputations), with similar proportional reductions observed in those with and without PAD. The absolute reduction in major vascular events was somewhat greater in participants with PAD at baseline (63 [SE 11] per 1000) than in those without PAD (50 [SE 7] per 1000: Fig 2). This reflected a greater absolute reduction in revascularizations among participants with PAD (42 [SE 9] per 1000) than among those without PAD (19 [SE 5] per 1000).

Effects on major vascular events in different circumstances among participants with PAD and other participants. The extreme statistical significance of the overall reduction in the rate of first major vascular events (z-score = 9.3), and the large number of events on which it is based, allows reliable assessment of the effects of treatment in various different categories of patient. The relative risk reduction among participants with or without diagnosed PAD at study entry was about a quarter in each of the subcategories studied (Fig 3 and Fig 4). In particular, among the 2701 patients with PAD but no pre-existing coronary disease, there was a significant 22% reduction in first major vascular events (327 [24.7%] simvastatin vs 420 [30.5%] placebo), which was similar to the effect in the other patients (heterogeneity $P = .9$: Fig 4). The propor-

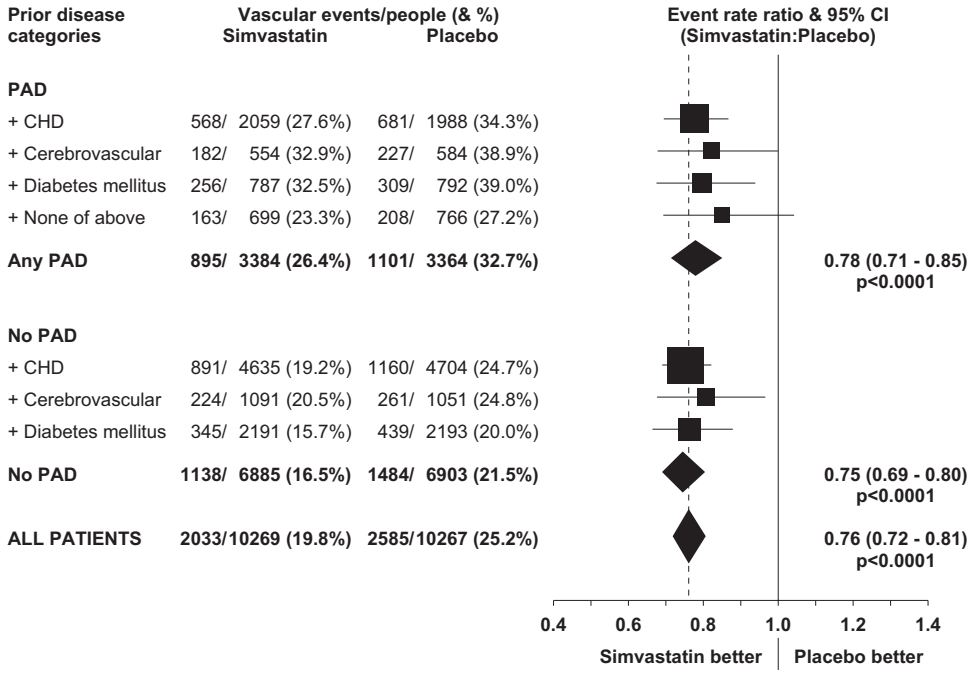

Fig 3. Effects of simvastatin allocation on major vascular events in prior disease subgroups. Symbols and conventions as in figure 1. There is no overlap between participants in "PAD" and "No PAD" baseline disease categories, but within each of these categories there is some overlap (and hence, some non-additivity).

tional risk reductions among all 6748 participants with PAD also appeared to be about a quarter, irrespective of their history of other vascular disease, diabetes, sex, or age (Fig 3 and Fig 4). Most notably, the proportional reduction in risk did not appear to be materially influenced by the pre-treatment lipid concentrations. So, for example, there was a highly significant 20% (6-32; $P = .006$) reduction amongst the 2034 PAD participants whose pre-treatment measurements of LDL cholesterol were below 3.0 mmol/L (116 mg/dL), which was similar to the highly significant 25% (13-34; $P < .0001$) reduction seen among other high-risk individuals recruited with LDL cholesterol below 3.0 mmol/L (Fig 4). Furthermore, this proportional reduction in risk was independent of the nature of participants' pre-existing peripheral arterial disease, with a highly significant 24% reduction (13-33; $P = .0002$) among the 2339 patients with prior peripheral arterial revascularizations/amputations and a similar, highly significant, 21% reduction (11-29; $P < .0001$) seen among the remaining 4409 patients with PAD.

Prevention of first and subsequent major vascular events among participants with PAD. Overall in this high-risk population of patients with and without PAD, 2585 (25.2%) placebo-allocated participants had a first major vascular event following randomisation during mean follow-up of 5 years, and allocation to simvastatin reduced this rate by about a quarter (Fig 1). But, these 2585 patients had 3697 first or subsequent major vascular events during this follow-up period, and the rate of these subsequent events was also reduced (Table III). Hence, whereas the 1.0 mmol/L reduction in LDL cholesterol observed on average during the study typically prevented 54 (SE 6) participants per 1000 from having at least one major vascular event, it prevented 91 (10) first or subsequent major vascular events per 1000 patients during this 5-year period of follow-up. These absolute benefits are even more marked in participants with PAD, in whom allocation to simvastatin prevented 63 (11) per 1000 from having at least one major vascular event, and prevented 116 (21) first or subsequent major vascular events.

Effects on peripheral vascular events subdivided by prior PAD and other characteristics. Overall, allocation to simvastatin was associated with a significant 16% (5-25; $P = .006$) proportional reduction in the rate of first peripheral vascular event following randomisation (479 [4.7%] simvastatin-allocated vs 561 [5.5%] placebo-allocated), which was not significantly influenced by baseline characteristics, including prior PAD, coronary disease, diabetes, age, or pre-treatment lipid levels (Fig 5). But, since the patients with PAD were at particularly high risk of peripheral vascular events, this relative risk reduction translated into much larger absolute reductions in participants with pre-existing PAD (20 [SE 8] per 1000) than in those without PAD (3 [SE 2] per 1000: Fig 5). The overall reduction in peripheral vascular events was due chiefly to a 20% relative reduction in non-coronary revascularizations (334 [3.3%] simvastatin vs 415 [4.0%] placebo; $P = .002$), reflecting significant reductions in both carotid endarterectomy or angioplasty (42 [0.4%] vs 82 [0.8%]; $P = .0003$) and in other non-coronary revascularization procedures

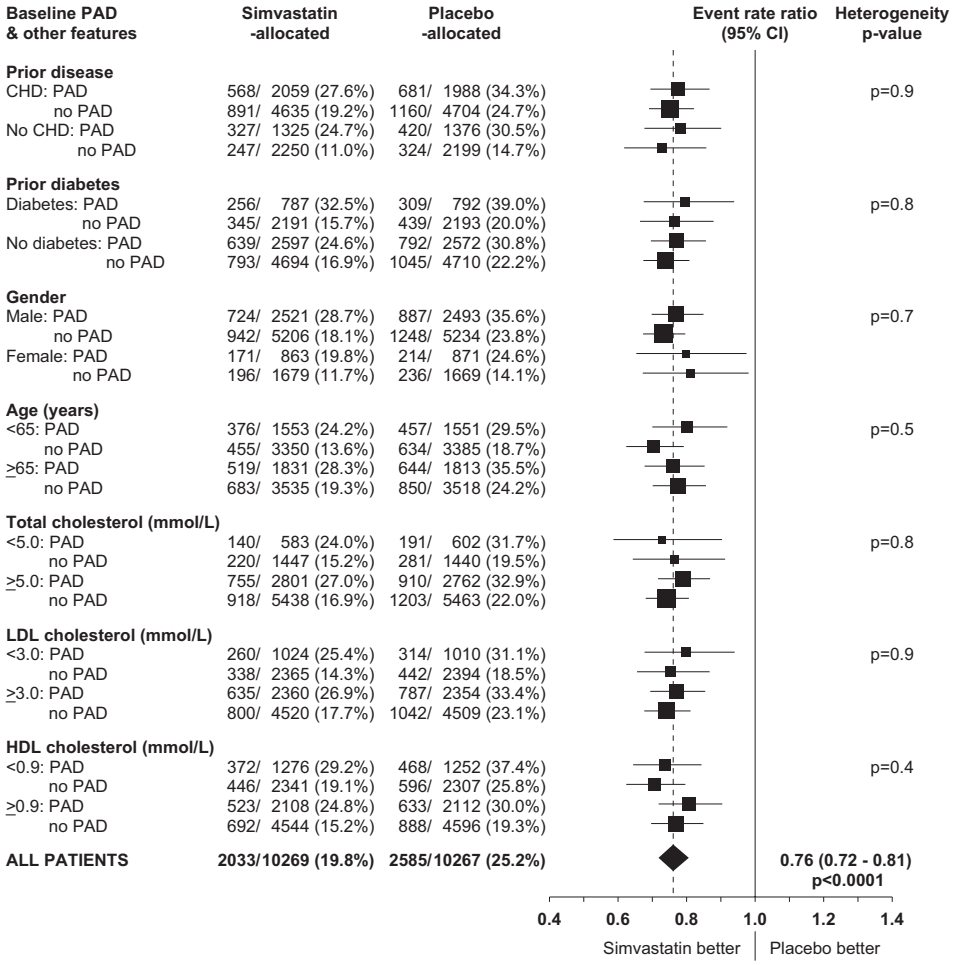

Fig 4. Effects of simvastatin allocation on first major vascular event in participants with or without PAD subdivided by other presenting features. Symbols and conventions as in Fig 1. Lipid categories relate to measured values at the initial screening visit prior to starting any statin therapy.

(295 [2.9%] vs 344 [3.4%]; $P = .04$). There was no apparent effect on the incidence of aneurysms repairs or deaths (120 [1.2%] vs 113 [1.1%]; $P = .7$) or of amputations (95 [0.9%] vs 103 [1.0%]; $P = .5$).

Safety. Simvastatin 40 mg daily was well tolerated during the trial, with no significant effect on liver enzymes or other adverse effects. Myopathy (muscle pain and/or weakness associated with an elevation in creatine kinase $>\times 10$ ULN) is a recognized rare side-effect of all statins, but the estimated excess risk with this dose of simvastatin was only about 1 per 10,000 patients per year.[17]

DISCUSSION

HPS provides the first reliable evidence that cholesterol-lowering statin therapy can produce substantial reductions of around one-quarter in the risk of major vascular events (heart attacks, strokes and revascularizations) among people with PAD, even if they do not already have manifest coronary disease. These beneficial effects are largely irrespective of baseline cholesterol and independent of, and

Table III. Effects of simvastatin allocation on first and all major vascular events in participants with or without PAD

Event	*Number of events*		*Events (SE) avoided per 1000 patients allocated simvastatin*
	Simvastatin-allocated	*Placebo-allocated*	
PAD			
First events	895	1101	63 (11)
All events	1327	1709	116 (21)
No PAD			
First events	1138	1484	50 (7)
All events	1436	1988	79 (10)
All patients			
First events	2033	2585	54 (6)
All events	2763	3697	91 (10)

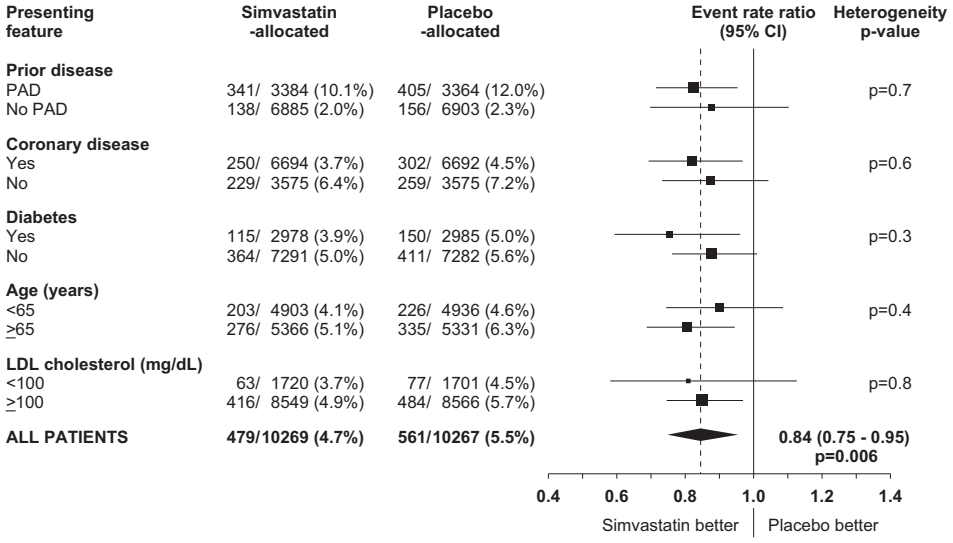

Fig 5. Effects of simvastatin allocation on first peripheral vascular event subdivided by presenting features. Symbols and conventions as in Fig 1. "Peripheral vascular event" was defined retrospectively as the first occurrence of a non-coronary revascularization, aneurysm repair, major amputation or PAD death.

hence additional to, those of other treatments used by such patients (including anti-hypertensive therapy and various other types of cardio-protective drugs). The absolute benefits in participants with PAD were at least as great as among the other high-risk groups studied, and involved a greater absolute reduction in non-coronary revascularization procedures.

Observational studies suggest that patients with overt PAD tend to be less well managed in terms of risk factor modification than patients with manifest coronary disease, despite their similar (or even higher) vascular risk, with as few as one-third of patients with PAD receiving statin therapy.[20] Prior to HPS, the role of lipid lowering therapy in the PAD population was unclear. A meta-analysis of "pre-statin" trials of lipid-lowering interventions[24] and a subsequent larger study of bezafibrate in men with PAD[25] did not provide clear evidence of benefit, and few patients with PAD were included in other randomized statin trials. By contrast, the present analyses of HPS show that continued statin treatment prevents not just the first occurrence of major vascular events in patients with PAD but also prevents subsequent events. Hence, among the 63 PAD participants per 1000 in HPS who avoided at least one major vascular event during 5 years of allocated simvastatin treatment, 116 first or subsequent major vascular events were avoided. Due in part to this effect on both first and subsequent events, an economic analysis of HPS has shown that 40 mg daily simvastatin should generally be cost-saving for patients with PAD.[26]

Because of its large size and the inclusion of almost 7000 individuals with pre-existing PAD, many more participants in HPS suffered peripheral vascular events than in any other randomized trial of cholesterol-lowering therapy (in which such events were either not recorded or occurred too infrequently to allow a reliable estimation of the effect of allocated therapy). Consequently, HPS is able to demonstrate reliably that statin therapy produces a definite reduction of around one-sixth in the risk of peripheral vascular events, both among patients with pre-existing PAD and among the other high-risk individuals studied who did not have diagnosed PAD. The magnitude of the relative reduction observed in peripheral vascular events is somewhat smaller than that observed in major coronary events, strokes or all revascularizations. This smaller effect on peripheral events may be due to the play of chance, or the more insidious nature of peripheral arterial disease (in which progression from intermittent claudication to critical limb ischemia and amputation is uncommon[27]), or the inclusion of outcomes that are not influenced by treatment. In particular, whereas allocation to simvastatin produced a 20% reduction in the rate of non-coronary revascularization procedures, there was no apparent effect on the incidence of amputations or fatal or repaired aneurysms (although, there were too few such events to rule out favorable effects). Long-term follow-up of HPS participants is ongoing, and it remains possible that evidence of benefit on these outcomes may still emerge.

Previous placebo-controlled trials and observational studies have suggested a beneficial effect of statin therapy on intermittent claudication by retarding symptom progression,[28-32] but the development or worsening of intermittent claudication was not systematically recorded in HPS. Despite this, the results of HPS clearly demonstrate that statin therapy should be considered for all patients with intermittent claudication to reduce their very significant risk of cardiovascular mortality and major morbidity. Furthermore, these intention-to-treat results probably underestimate the benefits of taking 40 mg simvastatin daily.

During HPS, the average difference in LDL cholesterol of about 1.0 mmol/L (39 mg/dL) that was observed between all those allocated simvastatin and all those allocated placebo represents only about two-thirds of the LDL cholesterol difference produced by the actual use of 40 mg simvastatin daily (due to the "drop-out" and "drop-in" rate of around one-sixth in those allocated simvastatin and placebo respectively). Similarly, the reduction of about a quarter in major vascular events in these intention-to-treat comparisons is likely to represent only about two-thirds of the risk reduction produced by actual compliance with this statin regimen. Hence, actual use of 40 mg simvastatin daily would lower LDL cholesterol by about 1.5 mmol/L (58 mg/dL) in this population and would probably reduce the rates of heart attacks, strokes, and revascularisations by about one-third and the rates of peripheral vascular events by about one-quarter.

HPS clearly demonstrates the benefits of cholesterol-lowering statin therapy in patients with PAD, safely producing highly significant reductions in cardiovascular morbidity and mortality in this high-risk group. In addition, statin use reduced the incidence of peripheral vascular events in all of the high-risk groups studied. These beneficial effects are largely irrespective of baseline cholesterol levels or other features. Consequently, statin therapy should be considered routinely for all people with, or at risk of, peripheral arterial disease.

AUTHOR CONTRIBUTIONS

Conception and design: RB, LB, KW, SP, JA, RC
Analysis and interpretation: RB, LB, KW, SP, JA, RC
Data collection: RB, LB, KW
Writing the article: RB, LB, KW, SP, JA, RC
Critical revision of the article: RB, LB, KW, SP, JA, RC
Final approval of the article: RB, LB, KW, SP, JA, RC
Statistical analysis: SP, KW
Obtained funding: RC, SP
Overall responsibility: RC

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Appendix

MRC/BHF Heart Protection Study Collaborative Group

Writing Committee–Richard Bulbulia, Louise Bowman, Karl Wallendszus, Sarah Parish, Jane Armitage, and Rory Collins.

Steering Committee–R Collins (principal investigator), T Meade (chairman), P Sleight (vice-chairman), J Armitage (clinical coordinator), S Parish and R Peto (statisticians), L Youngman (laboratory director), M Buxton, D de Bono (deceased), C George, J Fuller, A Keech, A Mansfield, B Pentecost, D Simpson, C Warlow; J McNamara and L O'Toole (MRC observers).

Data Monitoring Committee–R Doll (chairman; deceased), L Wilhelmsen (vice-chairman), K M Fox, C Hill, P Sandercock.

Collaborators–listed in reference 17.

DISCUSSION

Dr Matthew Dougherty (Philadelphia, Pa). There is no question, the statistics don't lie, that there is a benefit, but I'm impressed with your data offered per thousand patients. If I read it correctly, there is about a 2% absolute reduction in peripheral vascular events over a 5-year period, even in the PAD group, which seems like a pretty small number. And I wonder whether you have done any cost–benefit analysis to achieve that 0.4% per year reduction?

Dr Richard Bulbulia. Considering major vascular events, an economic analysis of HPS has shown that, at 2001 prices, 40 mg simvastatin is cost effective for all study participants. And, with patent expiry, the price of simvastatin is falling and it should be cost-saving for all HPS participants, particularly for those with PAD who actually derived the largest absolute benefits from statin therapy, with an absolute reduction in MVE of around 6%.

Dr Michael Conte (Boston, Mass). Congratulations to you and your coauthors for another outstanding contribution. For those who are not familiar with it, the original report from the Heart Protection Study was published a couple of years ago in *The Lancet*. This is an important follow-up to that study focused on our peripheral vascular patients, and I have a couple of questions. First, can you tell us if the presence or absence of diabetes affected the outcome in relation to statins? Was the apparent benefit of statins more or less enriched in the diabetic population?

Second, can you tell us a little bit more about the timing of the events in the PAD patients? Did you observe a uniform distribution of risk reduction over time, or was the effect seen mostly within the first year or two after randomization?

Finally, what can you tell us about antiplatelet therapy in the trial?

Dr Bulbulia. The beneficial effect of simvastatin was not influenced by the presence or absence of diabetes at baseline. A reduction in major vascular events was seen after around 1 year of treatment; however, in the recent Cholesterol Treatment Trialists Meta-analysis of over 91,000 participants, benefits emerge within the first year. Finally, the benefits seen with statin therapy were additional to, and therefore independent of, any other treatments, including antiplatelet agents.

Dr Eric Wahlberg (Stockholm, Sweden). Did you have a chance to look at the patients with PAD without cardiac disease at all? Could you also enlighten me if this paper differs anything from your previous publication from the HPS study, besides the analysis of the peripheral vascular events?

Dr Bulbulia. Around 2700 patients with PAD had no preexisting coronary artery disease at baseline, and they achieved similar proportional benefits as those with CAD and PAD. This presentation provides more detailed analyses of the PAD subgroup in HPS and emphasizes that all such patients should be on a statin. Observational studies suggest that less than one third of our patients are currently receiving appropriate lipid-lowering therapy. In addition, we have shown a reduction in peripheral vascular events with statin allocation, which has not been reported in any previous study.

Dr Thomas Lindsay (Toronto, Ontario, Canada). I would applaud this as probably the first study that demonstrates the benefit of statin therapy in a predominantly PAD group, so I think it's very important data. I have a couple of questions. First, what was the number needed to treat in order to prevent an event in the PAD subgroup vs the non-PAD subgroup?

Secondly, you said that the overall reduction in cholesterol was 1 mmol/L. Is there a better benefit with greater reductions in cholesterol level? Was there a dose-response in terms of the patients' benefit?

Third, many of these patients also have elevated triglycerides, which are in fact, much more difficult to treat. Was the effect of statin therapy dependent or independent of elevated triglyceride levels?

Dr Bulbulia. The number needed to treat to prevent a first major vascular event was 16 in the PAD subgroup and 20 in those without PAD. The effects of statin therapy were independent of baseline lipid profiles, including triglycerides. Finally, there is a trend towards using higher doses of statins in high-risk patients. Indeed the recent CTT meta-analysis suggests that an increased reduction in LDL cholesterol may result in increased benefits.

Dr Lindsay. What would you say is an appropriate LDL target level? As vascular surgeons take hold of risk reduction in our patient population, we really need to have some target to treat to.

Your first slide implied the lower the better. We see the cardiologists going from what used to be levels of 3 mmol/L down to 2 for LDL to now less than 2. Based on this data, what threshold would you recommend for trying to get a patient's LDL cholesterol to?

Dr Bulbulia. There should be no threshold for initiation of statin therapy. HPS was not a target-finding study, but results from some "more vs less" statin trials suggest that higher doses of statin therapy will reduce cardiac and noncardiac vascular events further. However, the question is whether the risks of side effects associated with statins, which are dose-dependent, justify this approach.

Dr Jacob Lustgarten (Chevy Chase, Md). Did you notice any morbidity and mortality benefits in patients who underwent surgery? Statins are increasingly associated with a plaque stabilization effect and a lower perioperative rate of adverse cardiac events, and even a lower stroke risk after carotid surgery. It seems almost like these patients should be on statins much the way β-blockers are used. You followed a large number of randomized patients. Did you look for this effect?

Dr Bulbulia. We have not performed such an analysis, but I am aware of the results of observational and smaller interventional studies suggesting improved outcomes with statin therapy in the perioperative period. However, our results clearly demonstrate that all these patients should be on a statin before, during, and after their operation.

INVITED COMMENTARY

William R. Hiatt, MD, *Denver, Colo*

Current guidelines give a class I recommendation to lower low-density lipoprotein (LDL) cholesterol levels below 100 mg/dL in all patients with peripheral artery disease (PAD) and a class IIa recommendation to lower the LDL cholesterol level below 70 mg/dL in patients who are at "very high risk of ischemic events."[1] High-risk PAD would be defined as more than one vascular bed involved—eg, a clinical history of concomitant coronary or cerebral vascular disease. The primary evidence for these recommendations comes from the original publication of the Heart Protection Study that evaluated the benefits of simvastatin in over 20,000 high-risk patients.[2] There were 6748 patients with PAD reported in the original publication, and these patients had a reduction in fatal and nonfatal cardiovascular events with simvastatin similar to that in patients with other forms of atherosclerosis. A recent meta-analysis of statin therapy in a broad population of high-risk patients demonstrated that there was a consistent benefit in reduction of risk of cardiovascular events across a wide population of patients and a wide range of baseline LDL cholesterol levels.[3] Thus there is a broad consensus to treat all patients at risk with statin drugs, regardless of their baseline cholesterol level.

The publication of the Heart Protection Study Collaborative Group in the *Journal of Vascular Surgery* focuses on the benefits of statin therapy specifically in the PAD population. The major new finding was a significant reduction in noncoronary revascularizations. Confirmatory findings were the consistency of the benefit across all populations studied (including patients with PAD who had no pre-existing coronary artery disease) and benefit regardless of baseline LDL cholesterol level. There was no benefit of the statin in preventing amputations, perhaps reflecting the end-stage pathophysiology of patients who suffer limb loss.

The message is clear. All patients with PAD are at high risk and meet criteria for statin therapy. The benefit of statin therapy is primarily systemic (prevention of major cardiovascular events) but also local (reduction of the need for revascularization).

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Table II, online only. Average use of statin (study or non-study), and average plasma LDL cholesterol concentrations, during follow-up

Presenting features	*Use of study/ non-study statin (%)*			*Plasma LDL cholesterol (mmol/L)*		
	Simvastatin-allocated	*Placebo-allocated*	*Absolute difference**	*Simvastatin-allocated*	*Placebo-allocated*	*Absolute difference**
Prior CHD						
CHD: PAD	84%	21%	63%	2.4	3.2	–0.8
no PAD	87%	20%	67%	2.3	3.2	–1.0
No CHD: PAD	82%	12%	70%	2.4	3.4	–1.0
no PAD	83%	11%	72%	2.2	3.2	–1.0
Age (years)						
<65: PAD	83%	21%	62%	2.4	3.3	–0.9
no PAD	85%	20%	65%	2.3	3.2	–0.9
≥65: PAD	83%	14%	69%	2.3	3.3	–0.9
no PAD	86%	15%	71%	2.2	3.3	–1.1
Total cholesterol (mmol/L)						
<5.0: PAD	81%	5%	75%	1.8	2.6	–0.8
no PAD	84%	5%	79%	1.7	2.7	–0.9
≥5.0: PAD	84%	20%	64%	2.5	3.4	–0.9
no PAD	86%	21%	66%	2.4	3.4	–1.0
LDL cholesterol (mmol/L)						
<3.0: PAD	81%	7%	74%	1.9	2.7	–0.8
no PAD	84%	8%	76%	1.8	2.8	–0.9
≥3.0: PAD	84%	22%	62%	2.6	3.5	–0.9
no PAD	87%	22%	64%	2.5	3.5	–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 40mg simvastatin daily can be estimated as the ratio of these two columns (for example, –1.0/67% = –1.5 mmol/L).