

# C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20 536 patients in the Heart Protection Study

Heart Protection Study Collaborative Group\*

## Summary

**Background** It has been suggested that inflammation status, as assessed by C-reactive protein (CRP) concentration, modifies the vascular protective effects of statin therapy. In particular, there have been claims that statins might be more beneficial in people with raised CRP concentrations, and might even be ineffective in people with low concentrations of both CRP and LDL cholesterol. This study aimed to test this hypothesis.

**Methods** In 69 UK hospitals, 20 536 men and women aged 40–80 years at high risk of vascular events were randomly assigned to simvastatin 40 mg daily versus matching placebo for a mean of 5·0 years. Patients were categorised into six baseline CRP groups (<1·25, 1·25–1·99, 2·00–2·99, 3·00–4·99, 5·00–7·99, and ≥8·00 mg/L). The primary endpoint for subgroup analyses was major vascular events, defined as the composite of coronary death, myocardial infarction, stroke, or revascularisation. Analysis was by intention to treat. This study is registered, number ISRCTN48489393.

**Findings** Overall, allocation to simvastatin resulted in a significant 24% (95% CI 19–28) proportional reduction in the incidence of first major vascular event after randomisation (2033 [19·8%] allocated simvastatin vs 2585 [25·2%] allocated placebo). There was no evidence that the proportional reduction in this endpoint, or its components, varied with baseline CRP concentration (trend  $p=0\cdot41$ ). Even in participants with baseline CRP concentration less than 1·25 mg/L, major vascular events were significantly reduced by 29% (99% CI 12–43,  $p<0\cdot0001$ ; 239 [14·1%] vs 329 [19·4%]). No significant heterogeneity in the relative risk reduction was recorded between the four subgroups defined by the combination of low or high baseline concentrations of LDL cholesterol and CRP ( $p=0\cdot72$ ). In particular, there was clear evidence of benefit in those with both low LDL cholesterol and low CRP (27% reduction, 99% CI 11–40,  $p<0\cdot0001$ ; 295 [15·6%] vs 400 [20·9%]).

**Interpretation** Evidence from this large-scale randomised trial does not lend support to the hypothesis that baseline CRP concentration modifies the vascular benefits of statin therapy materially.

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## Introduction

Inflammation is thought to contribute to the pathogenesis of coronary heart disease.<sup>1</sup> C-reactive protein (CRP), an acute phase reactant synthesised by the liver, is the most extensively studied systemic marker of inflammation. Results from a meta-analysis<sup>2</sup> of individual participant data from 54 prospective observational studies showed that CRP concentration was associated with the risk of coronary heart disease, ischaemic stroke, and vascular and non-vascular mortality. However, associations with ischaemic vascular diseases were explained largely by conventional risk factors (eg, CRP is positively correlated with smoking, diabetes, physical inactivity, blood pressure, body-mass index, non-HDL cholesterol, and triglycerides<sup>3</sup>), and so they might not reflect causality (which is supported by genetic-epidemiological studies<sup>3</sup>). Nonetheless, the ability of CRP to predict vascular risk means that it might still be useful as a biomarker to identify individuals who would particularly benefit from therapies to reduce risk.<sup>4</sup>

Some,<sup>5,6</sup> but not all,<sup>7</sup> subgroup analyses undertaken in previous randomised trials of statin therapy have suggested that the vascular benefits might be greater in the presence of inflammation than in its absence. It has even been suggested that people who have low concentrations of both LDL cholesterol and CRP might not benefit much from statin therapy.<sup>8</sup> The JUPITER trial<sup>9</sup> randomly allocated 17802 apparently healthy men and women with LDL cholesterol concentrations less than 130 mg/L (3·4 mmol/L) but CRP concentrations 2·0 mg/L or greater to receive either rosuvastatin 20 mg daily or matching placebo. Allocation to rosuvastatin reduced LDL cholesterol at 1 year by about 50% (ie, 1·2 mmol/L) and CRP by about 40% (1·3 mg/L) and, during median treatment duration of about 2 years, there was a significant 44% reduction in the primary composite endpoint of myocardial infarction, stroke, arterial revascularisation, admission to hospital for unstable angina, or death from cardiovascular causes.<sup>9</sup> It has been suggested that this large relative risk reduction is greater than might have been expected given the achieved LDL cholesterol reduction,<sup>9,10</sup> raising the possibility that the

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See [Comment](#) page 441

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	<1.25 mg/L (n=3397)	1.25–1.99 mg/L (n=2729)	2.00–2.99 mg/L (n=2943)	3.00–4.99 mg/L (n=3766)	5.00–7.99 mg/L (n=2562)	≥8.00 mg/L (n=3048)	Not measured (n=2091)
Log CRP (log mg/L)	-0.3 (0.5)	0.5 (0.1)	0.9 (0.1)	1.3 (0.1)	1.8 (0.1)	2.7 (0.5)	..
Age (years)	62.6 (9.0)	63.8 (8.5)	64.1 (8.3)	64.4 (8.1)	64.2 (8.0)	64.3 (8.1)	64.7 (8.6)
Men	80.8%	79.2%	78.1%	76.6%	71.9%	68.6%	68.5%
Previous disease*							
MI	42.4%	42.7%	44.1%	43.3%	42.7%	41.9%	29.0%
Other CHD without MI	23.4%	24.8%	24.6%	24.6%	23.0%	23.2%	21.8%
No CHD	34.2%	32.5%	31.3%	32.1%	34.3%	34.9%	49.2%
Cerebrovascular disease	14.2%	14.9%	15.2%	16.0%	16.2%	17.3%	18.9%
Peripheral vascular disease	22.9%	28.6%	30.4%	35.5%	39.0%	40.4%	34.8%
Diabetes	29.4%	27.3%	28.2%	27.8%	29.5%	28.8%	34.1%
Drug use*							
ACE inhibitors	15.5%	17.8%	19.7%	20.2%	21.9%	21.1%	20.0%
β blockers	26.3%	26.9%	26.8%	26.0%	25.8%	23.0%	25.0%
Diuretics	15.8%	19.7%	23.9%	25.1%	29.9%	32.3%	25.3%
Any treatment for hypertension	34.3%	39.5%	41.0%	41.8%	44.2%	45.3%	43.8%
Aspirin	65.7%	66.3%	65.0%	64.5%	63.1%	60.9%	54.2%
Current cigarette smoker*	8.8%	10.2%	11.9%	14.7%	19.1%	20.0%	15.9%
Physical measurements*							
SBP (mm Hg)	141.3 (23.1)	143.7 (23.0)	144.4 (23.0)	145.1 (23.0)	144.9 (23.0)	145.4 (23.0)	146.6 (23.0)
DBP (mm Hg)	80.0 (12.2)	81.2 (12.1)	81.1 (12.1)	81.9 (12.1)	81.6 (12.1)	81.3 (12.2)	83.0 (12.2)
BMI (kg/m <sup>2</sup> )	25.7 (4.2)	26.9 (4.2)	27.5 (4.2)	28.1 (4.2)	28.6 (4.2)	28.8 (4.2)	27.9 (4.2)
Non-fasting blood lipids*							
LDL cholesterol (mmol/L)	3.22 (0.80)	3.32 (0.80)	3.36 (0.80)	3.43 (0.80)	3.46 (0.80)	3.39 (0.80)	3.38 (0.80)
HDL cholesterol (mmol/L)	1.16 (0.31)	1.09 (0.30)	1.06 (0.30)	1.03 (0.30)	1.01 (0.30)	1.00 (0.30)	1.05 (0.30)
Log triglycerides (log mmol/L)	0.39 (0.56)	0.53 (0.56)	0.60 (0.56)	0.64 (0.56)	0.66 (0.56)	0.59 (0.56)	0.58 (0.56)
Randomised to simvastatin	50.0%	50.1%	51.1%	49.2%	50.0%	49.7%	50.3%
Randomised to vitamins	49.7%	50.8%	50.7%	49.4%	50.4%	49.7%	49.6%

Data are mean (SD) or percentage of patients. CRP=C-reactive protein. MI=myocardial infarction. CHD=coronary heart disease. ACE=angiotensin-converting enzyme. SBP=systolic blood pressure. DBP=diastolic blood pressure. BMI=body-mass index. \*Adjusted for age and sex differences between groups.

**Table 1: Patient characteristics by baseline concentration of CRP**

benefits of statins might be proportionally greater in people with high CRP concentrations. Secondary analyses of the JUPITER trial did not record any evidence that the effect of rosuvastatin on vascular events differed according to baseline CRP concentration,<sup>11</sup> but these analyses included only three baseline groups for CRP (because of the relatively small number of events) and were not able to assess the effect in people with CRP concentration less than 2.0 mg/L (because they were not eligible for the trial).

The Heart Protection Study (HPS) is, to date, the largest randomised trial of statin therapy and was undertaken in high-risk patients in whom large numbers of major vascular events occurred during the study treatment period. This study tested the hypothesis that the effects of statin therapy differ according to baseline concentrations of CRP and LDL cholesterol.

## Methods

### Study design and participants

Details of the objectives, design, and methods of HPS have been previously reported,<sup>12,13</sup> and are summarised in

this Article. Between 1994 and 1997, 20 536 men and women aged 40–80 years at high risk of vascular events were recruited from 69 UK hospitals. Participants had to have a previous diagnosis of coronary disease, occlusive disease of non-coronary arteries, diabetes (type 1 or 2), or, for men 65 years and older, be receiving drug treatment for hypertension. The exclusion criteria are listed in the study protocol. Ethics approval was obtained from relevant authorities.

At the initial screening visit, nurses recorded information about past medical history and other relevant factors; measured the patient's height, weight, and blood pressure; and took a non-fasting blood sample. Potentially eligible patients were given information about the study and asked for their written agreement to participate. Consenting participants entered a run-in phase, consisting of 4 weeks of placebo followed by 4–6 weeks of 40 mg simvastatin daily. Compliant individuals who did not have a major problem during the run-in and remained eligible were then randomised into the study and had their current medication recorded.

For more about the HPS protocol see <http://www.hpsinfo.org>

	n	Change in mean concentration from baseline to final follow-up				
		Placebo	Simvastatin	Absolute difference	Percentage difference	Difference in SDs*
<b>Changes in LDL cholesterol (mmol/L)</b>						
All patients	2727	-0.19 (0.02)	-1.04 (0.02)	-0.85 (0.03)	-25%	-1.1
Baseline CRP (mg/L)						
<1.25	539	-0.11 (0.05)	-0.98 (0.04)	-0.87 (0.07)	-26%	-1.1
1.25-1.99	429	-0.23 (0.06)	-1.00 (0.06)	-0.77 (0.08)	-23%	-1.0
2.00-2.99	460	-0.23 (0.06)	-1.11 (0.05)	-0.88 (0.08)	-26%	-1.1
3.00-4.99	547	-0.25 (0.06)	-1.12 (0.05)	-0.87 (0.07)	-26%	-1.1
5.00-7.99	377	-0.19 (0.07)	-0.97 (0.06)	-0.79 (0.09)	-24%	-1.0
≥8.00	375	-0.13 (0.08)	-1.05 (0.06)	-0.91 (0.10)	-27%	-1.1
<b>Changes in log CRP (log mg/L)</b>						
All patients	2727	-0.04 (0.03)	-0.36 (0.03)	-0.32 (0.04)	-27%	-0.3
Baseline LDL cholesterol (mmol/L)†						
<2.69	587	-0.08 (0.06)	-0.37 (0.07)	-0.30 (0.09)	-26%	-0.3
2.69-3.13	550	-0.05 (0.06)	-0.35 (0.07)	-0.30 (0.09)	-26%	-0.3
3.14-3.52	538	-0.09 (0.06)	-0.44 (0.06)	-0.35 (0.09)	-30%	-0.4
3.53-4.01	548	0.03 (0.06)	-0.41 (0.06)	-0.44 (0.09)	-36%	-0.4
≥4.02	504	-0.02 (0.07)	-0.22 (0.06)	-0.20 (0.09)	-18%	-0.2

Data in parentheses are SE. Final year follow-up sample was taken at a mean of 4.6 years. CRP=C-reactive protein. \*SD at screening (0.80 mmol/L for LDL cholesterol; 1.00 log mg/L for log CRP) in all 2727 people with data for concentrations of LDL cholesterol and CRP at baseline and final year of follow-up. †Separated into approximate fifths of the baseline distribution in all 20 536 randomised patients.

**Table 2: Effect of simvastatin allocation on changes in concentrations of LDL cholesterol and CRP between baseline and final year of follow-up**

### Randomisation and masking

Participants were randomly assigned to receive 40 mg simvastatin daily or matching placebo (and, separately, with a factorial design, to receive antioxidant vitamins or matching placebo capsules<sup>14</sup>), and were followed up for a mean of 5.0 years. Randomisation was done centrally with use of a minimisation algorithm. Study outcomes were reported and coded in a masked manner.<sup>12</sup>

### Procedures

Screening blood samples were cooled and sent by overnight courier to the coordinating centre laboratory for immediate separation and assay, and for long-term storage in liquid nitrogen. After an average of 4.6 years, non-fasting blood was collected from all participants during the final year of follow-up. Lipid fractions (including LDL cholesterol measured directly) at baseline and during follow-up were analysed as previously reported.<sup>13</sup> CRP was measured with a high-sensitivity assay with an Olympus CRP Latex OSR 6199 (Olympus Diagnostics, Melville, NY, USA) in plasma samples collected and stored at baseline from all participants and during the final year from a subset of participants. Within-assay and between-assay coefficients of variation were less than 5% for baseline measurements of LDL cholesterol and CRP (data not shown).

Participants were to be seen in the study clinics at regular intervals throughout follow-up (with non-attending patients followed up by telephone or through their family doctor). At every follow-up, information was recorded about any suspected myocardial infarction, stroke, vascular

procedure, or other serious adverse event (including admission to hospital for any reason). Further details were sought from general practitioners about all reports that might relate to vascular events, cancers, or deaths, and from UK national registries about cancers and certified causes of death. The primary prespecified endpoint for subgroup analyses was major vascular events, which were defined as major coronary events (ie, coronary death and non-fatal myocardial infarction), any stroke (fatal or non-fatal), or coronary or non-coronary revascularisation. During the study, 20 469 participants (99.7%) had complete follow-up for both mortality and morbidity.

### Statistical analysis

Patients were categorised into six baseline CRP groups (<1.25, 1.25-1.99, 2.00-2.99, 3.00-4.99, 5.00-7.99, and ≥8.00 mg/L), each including about 3000 patients (2091 participants did not have CRP measured at baseline). The effects of allocation to simvastatin on the incidence of particular outcomes were analysed with log-rank methods both overall and separately within each CRP group (and for the group without values).  $\chi^2$  tests for linear trend in the proportional effects of simvastatin across the six CRP groups were undertaken. Subgroup analyses of a previous trial<sup>8</sup> had generated the hypothesis that statins might not have much effect in people with baseline concentrations of LDL cholesterol and CRP that are both low (defined by the median values in that trial: LDL cholesterol <3.86 mmol/L and CRP <1.6 mg/L). To test that hypothesis in HPS, log-rank analyses were undertaken

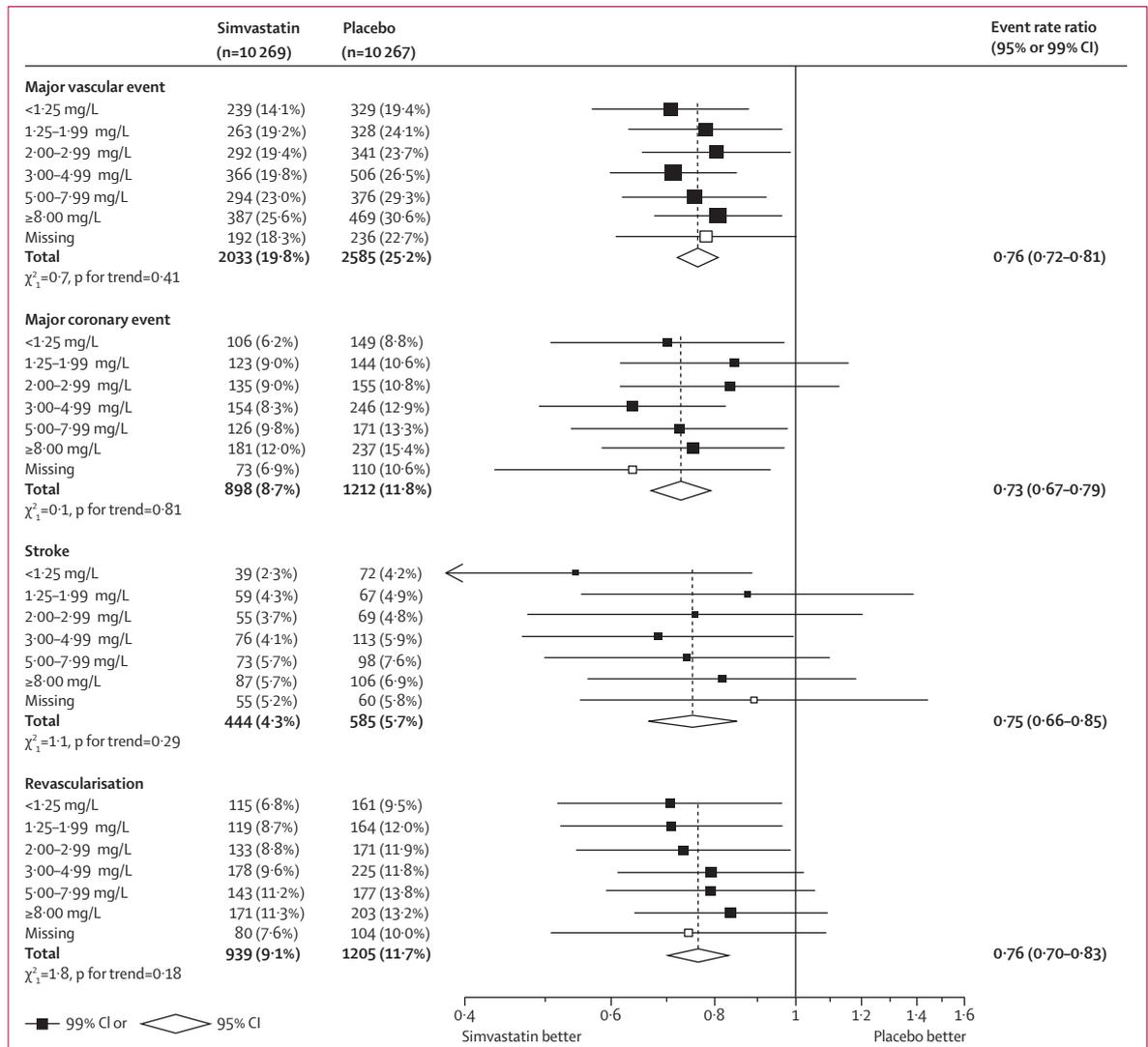


Figure 1: Effect of simvastatin allocation on vascular events by baseline concentration of C-reactive protein

of the effect of allocation to simvastatin on major vascular events in the four groups that were defined jointly by the same median concentrations of LDL cholesterol and CRP. To make some allowance for multiple comparisons, only summary rate ratios or reductions are presented with 95% CIs, whereas those for subgroup analyses are presented with 99% CIs. All statistical tests were two-sided and done on an intention-to-treat basis.

This study is registered, number ISRCTN48489393.

**Role of the funding source**

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All members of the Writing Committee agreed to submit the paper for publication. JE, DB, and SP had full access to all the data in the study.

**Results**

Baseline CRP concentration was substantially skewed (skewness coefficient 5.9), with a median of 3.07 mg/L (IQR 1.59–5.85). Table 1 shows the patient characteristics for each baseline CRP group. In this selected trial population, participants with higher baseline CRP concentrations were more likely to be women, to have had a diagnosis of peripheral vascular disease, to be taking diuretic drugs, and to be a current smoker than were those with lower baseline CRP concentrations (table 1). Participants with high baseline CRP concentrations had higher mean body-mass index, LDL cholesterol, and triglyceride concentration, and lower mean HDL cholesterol concentration (although the age-adjusted and sex-adjusted correlation between LDL cholesterol and log CRP concentration was weak;  $r=0.08$ ).

As previously reported,<sup>12</sup> allocation to simvastatin produced a mean difference in LDL cholesterol between randomised groups during the trial of 1.0 mmol/L. In the selected subset of 2727 patients with LDL cholesterol and CRP measured at both screening and during the final year of follow-up, allocation to simvastatin produced a mean difference between randomised groups of 0.85 mmol/L (SE 0.03 mmol/L) in LDL cholesterol, which is a 25% mean proportional reduction, and of 0.32 log mg/L (SE 0.04 log mg/L) in log CRP, which is a 27% mean proportional reduction (both  $p < 0.0001$ ; table 2). These differences represented SD changes of 1.1 for LDL cholesterol and 0.3 for log CRP; thus, the reduction in relation to overall variability was much greater for LDL cholesterol than for CRP. The estimated changes in LDL cholesterol did not differ significantly by baseline CRP concentration, and nor did the estimated changes in CRP differ significantly by baseline LDL cholesterol (table 2; age-adjusted and sex-adjusted correlation between changes in LDL cholesterol and changes in log CRP=0.14).

Overall, allocation to simvastatin produced a significant 24% (95% CI 19–28) proportional reduction in the incidence of first major vascular event after randomisation.<sup>12</sup> There was no significant trend in the proportional risk reduction with increasing baseline CRP (figure 1), with significant reductions in each of the baseline CRP groups, including in participants with CRP concentration less than 1.25 mg/L (29% risk reduction, 99% CI 12–43;  $p < 0.0001$ ). Indeed, even in those with baseline CRP concentration less than 1 mg/L, there was a significant 27% (99% CI 5–44) reduction in risk [166 [13.7%] allocated to simvastatin vs 218 [18.3%] allocated to placebo;  $p = 0.0022$ ).

Allocation to simvastatin reduced the incidence of first major coronary event by 27% (95% CI 21–33), of first stroke by 25% (15–34), and of first revascularisation by 24% (17–30), with no significant trend in the proportional risk reduction with increasing baseline CRP concentration for any of these outcomes (figure 1). There was also no significant trend in the proportional reduction in vascular death with increasing baseline CRP (figure 2). Although a marginally significant trend in the proportional reduction in non-vascular mortality was noted with increasing CRP concentration (figure 2), this result was not significant after taking into account the number of trend tests done (Bonferroni corrected  $p = 0.10$ ).

To test the hypothesis that the proportional effect of statin therapy on vascular events might differ according to whether individuals have greater than mean concentrations of LDL cholesterol, CRP, both, or neither,<sup>8</sup> participants were categorised into four groups defined by the median concentrations of LDL cholesterol (3.86 mmol/L) and CRP (1.6 mg/L) in the trial that generated the hypothesis. In HPS, there was no significant heterogeneity in the proportional reduction in major vascular events between these four groups (figure 3). In particular, the proportional risk reduction in participants with low LDL cholesterol and low CRP (27%, 99% CI 11–40;  $p < 0.0001$ ) was statistically similar to that in participants with high LDL cholesterol and high CRP (23%, 10–35;  $p < 0.0001$ ). Even when the threshold used to define low LDL cholesterol was reduced to 2.8 mmol/L (which was the median baseline concentration in the JUPITER trial<sup>9</sup>), the proportional reduction in major vascular events in participants with low LDL cholesterol and low CRP (92 [13.6%] vs 128 [18.2%]; risk reduction 0.73, 99% CI 0.52–1.04;

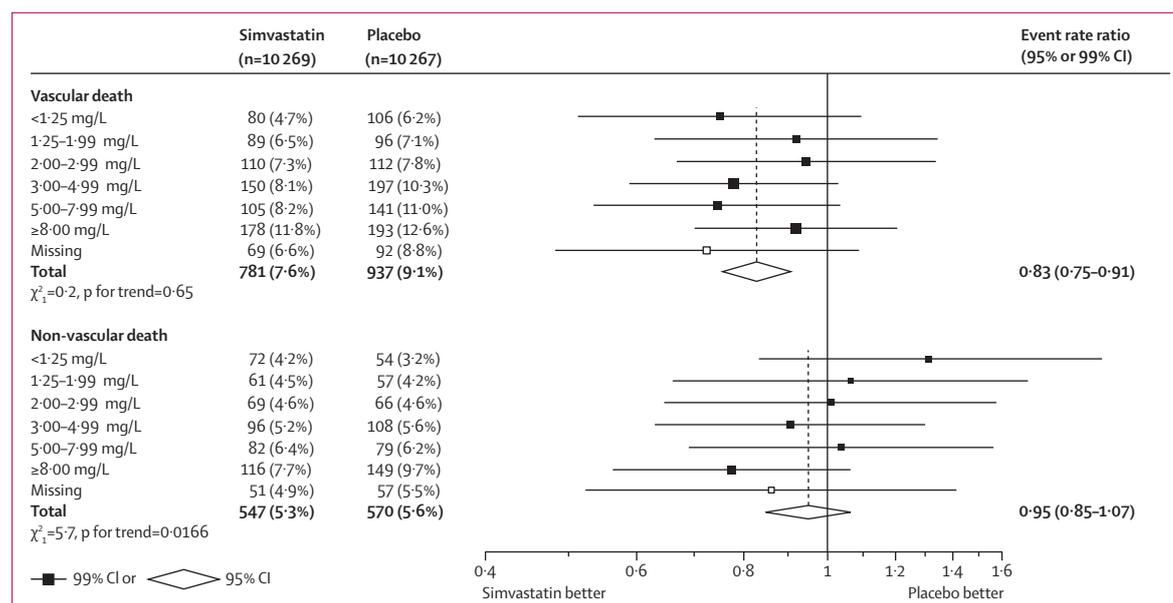
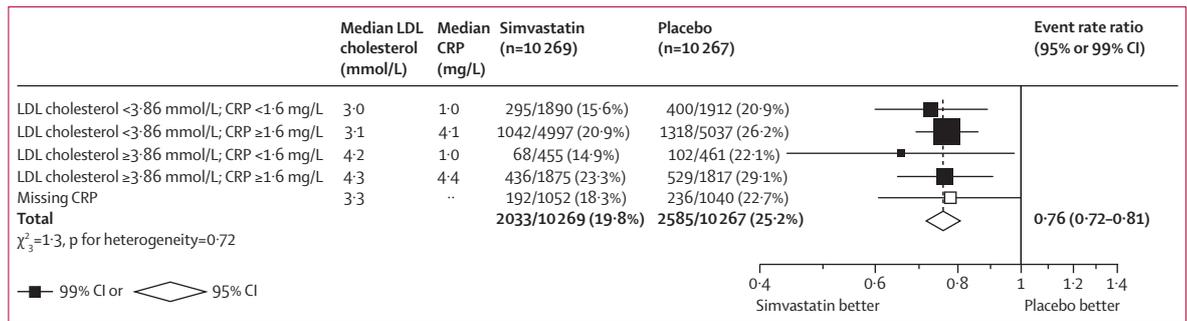


Figure 2: Effect of simvastatin allocation on vascular and non-vascular death by concentration of baseline C-reactive protein



**Figure 3:** Effect of simvastatin allocation on first major vascular event during follow-up by baseline concentrations of LDL cholesterol and CRP. Test for heterogeneity between four groups, excluding participants with missing data for baseline CRP concentration. Threshold values used to define low and high concentrations of LDL cholesterol and CRP are from the median values in the hypothesis-generating trial.<sup>8</sup> CRP=C-reactive protein.

p=0.0213) was still similar to the reduction recorded overall (figure 3).

**Discussion**

In this study of more than 20 000 people at high risk of vascular events, 5.0 years of statin therapy reduced the risk of a major vascular event by a quarter, but there was no indication that the proportional risk reduction was larger in those with higher baseline CRP concentration. Indeed, even in participants with baseline CRP concentration less than 1.25 mg/L, or with low baseline concentrations of both LDL cholesterol and CRP, there were significant reductions in the risks of major vascular events. Furthermore, the proportional reduction in major vascular events in HPS did not differ significantly between participants with different baseline concentrations of other circulating inflammatory markers, such as lipoprotein-associated phospholipase A<sub>2</sub> (a pro-inflammatory enzyme expressed in rupture-prone atherosclerotic plaque)<sup>15</sup> or albumin (a liver-derived negative acute-phase reactant; results available on request). Hence, the present hypothesis-testing analysis (which is based on large numbers of major vascular events) does not lend support to the suggestion from hypothesis-generating studies (which include far fewer vascular events) that the beneficial effects of statin therapy are affected by baseline CRP concentration or, more generally, by inflammation status (panel).

The proportional reduction in the risk of major vascular events with statin therapy seems to be directly related to the absolute reduction in LDL cholesterol that is achieved.<sup>16-18</sup> A meta-analysis<sup>17</sup> of 25 large randomised trials (including more than 150 000 participants) estimated that 80-90% of the heterogeneity between their results could be explained by differences in the reduction of LDL cholesterol (87% for major coronary events and 84% for major vascular events), which contrasts with other interpretations from selected trials.<sup>8,19</sup> In addition to the lipid-mediated effects of statins, substantial interest has been generated in the possibility of lipid-independent pleiotropic effects,

perhaps by stabilisation of plaques through various anti-inflammatory mechanisms.<sup>20,21</sup>

In apparent support of this hypothesis, analyses within some trials have shown that participants who achieve low CRP concentration on statin therapy, irrespective of their achieved LDL cholesterol concentration, have lower coronary event rates than do those who do not achieve low CRP.<sup>22,23</sup> However, such comparisons of outcome in participants allocated to statins who achieve particular CRP concentrations and in those who do not versus the outcome in all of the participants allocated to placebo combined (irrespective of whether or not they would have achieved those CRP concentrations if they had been given statin therapy) are not randomised and, hence, prone to bias. For example, the observed risk differences could be attributable to inherent differences between the types of participant who achieve such CRP concentrations and those who do not, rather than differences that are really due to the CRP reductions.<sup>24,25</sup> Moreover, investigators of a meta-analysis<sup>26</sup> of 23 placebo-controlled trials have reported that at least 90% of the CRP reduction detected with therapies to lower LDL cholesterol (mostly statins) can be explained by reductions in LDL cholesterol. Because the proportional reduction in vascular events associated with the reduction in LDL cholesterol achieved in the JUPITER trial<sup>9</sup> was larger than was expected from previous statin trials,<sup>16</sup> it has been suggested that it provides support for non-lipid benefits of statins. But, JUPITER was terminated early because of the emergence of clear evidence of benefit, so the size of the real effects of treatment might well have been overestimated.<sup>27</sup>

The present hypothesis-testing analysis has several strengths. First, HPS has larger numbers of major vascular events than any other randomised trial of statin therapy, so it has greater statistical power to detect differences in effect size in different subgroups. Second, it can assess the effects of statin therapy across a wide range of baseline concentrations of CRP or LDL cholesterol because participants were recruited with no constraints on the values of these factors. Third, the results are applicable not only to the wide range of people with pre-existing vascular disease who were recruited

**Panel: Research in context****Systematic review**

Electronic searches of Medline, PubMed, and Scopus, supplemented by hand searches of reference lists of review articles and meta-analyses, identified four trials<sup>6-8,11</sup> that had previously estimated the effect of statin therapy by baseline concentration of C-reactive protein (CRP). These studies were all of high quality based on blinding of patients, use of intention-to-treat analyses, details about completeness of follow-up, the type of intervention, reporting of the patient population, and outcome reporting. However, they each included small numbers of cardiovascular events.

**Interpretation**

The large numbers of major vascular events in the Heart Protection Study (HPS) allows a reliable test of the hypothesis that the effects of statin therapy differ according to baseline CRP concentration. The results do not lend support to the suggestion that the beneficial effects of statin therapy are affected by baseline CRP concentration or, more generally, by inflammation status. The results could be applicable to all statins (not only simvastatin) and are likely to be applicable to a wide range of people with and without pre-existing vascular disease.

into HPS, but also to people without known vascular disease (as in JUPITER), since the proportional benefits of statins are as large in primary prevention.<sup>16,18</sup> In this respect, it is worth noting that people who have events during only a few years of treatment (eg, average time to events in a 4-year trial is only about 2 years) are most likely to have had pre-existing vascular disease, irrespective of whether they were derived from high-risk secondary prevention or low-risk primary prevention populations.

Because patients in the hypothesis-generating trials were allocated to pravastatin and lovastatin, and in JUPITER to rosuvastatin, the results from HPS, which studied simvastatin, might not necessarily be generalisable to other statins.<sup>28</sup> But, the differential effect of different statins on the risk of major vascular events can be largely, if not wholly, explained by differences in reduction in LDL cholesterol.<sup>16-18</sup> Moreover, the 27% mean CRP reduction in HPS that was associated with a 0.85 mmol/L reduction in LDL cholesterol in participants allocated to simvastatin (table 2) is about the same per mmol/L LDL cholesterol reduction as the 37% mean CRP reduction in JUPITER, which was associated with a 1.2 mmol/L reduction in LDL cholesterol in those allocated to rosuvastatin.<sup>9</sup> In the CORONA trial,<sup>6</sup> rosuvastatin seemed to produce beneficial effects on vascular events in patients with baseline CRP greater than 2 mg/L and not in those with lower concentrations. But, those analyses were retrospective and based on small numbers of events in people with CRP concentration less than 2 mg/L, so they might be indicative of data-dependent emphasis and chance.<sup>6</sup>

Baseline CRP concentration did not seem to modify the effects of rosuvastatin in JUPITER (although people with CRP <2 mg/L were excluded from this trial and it could only consider three CRP groups because of the relatively small number of events),<sup>11</sup> or the effects of different doses of simvastatin in the A to Z trial<sup>7</sup> (albeit with very limited statistical power). Consequently, the findings in HPS, that reducing LDL cholesterol with simvastatin reduces the risk of major vascular events to a similar extent irrespective of presenting CRP concentrations (including among individuals with low concentrations of both CRP and LDL cholesterol), are probably broadly generalisable to other statins.

**Contributors**

S Parish, J Armitage, and R Collins were responsible for the study concept and design. J Armitage and R Collins acquired data. J Emberson, D Bennett, E Link, and S Parish did the statistical analysis. J Emberson drafted the report. All authors contributed to the interpretation of data and critically revised the report for important intellectual content.

**MRC/BHF Heart Protection Study Collaborative Group**

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**Conflicts of interest**

The CTSU has a policy of not accepting honoraria or other payments directly or indirectly from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. JD has received research grants, consultancy, and board membership fees from GlaxoSmithKline, Merck, Novartis, and Pfizer.

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