# Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial

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## Summary

**Background** **Statins lower high-sensitivity C-reactive protein (hsCRP) and cholesterol concentrations, and hypothesis generating analyses suggest that clinical outcomes improve in patients given statins who achieve hsCRP concentrations less than 2 mg/L in addition to LDL cholesterol less than 1·8 mmol/L (<70 mg/dL). However, the benefit of lowering both LDL cholesterol and hsCRP after the start of statin therapy is controversial. We prospectively tested this hypothesis.**

**Methods** **In an analysis of 15 548 initially healthy men and women participating in the JUPITER trial (87% of full cohort), we prospectively assessed the effects of rosuvastatin 20 mg versus placebo on rates of non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularisation, or cardiovascular death (prespecified endpoints) during a maximum follow-up of 5 years (median 1·9 years), according to on-treatment concentrations of LDL cholesterol (≥1·8 mmol/L or <1·8 mmol/L) and hsCRP (≥2 mg/L or <2 mg/L). We included all events occurring after randomisation. This trial is registered with ClinicalTrials.gov, number NCT00239681.**

**Findings** **Compared with placebo, participants allocated to rosuvastatin who achieved LDL cholesterol less than 1·8 mmol/L had a 55% reduction in vascular events (event rate 1·11 *vs* 0·51 per 100 person-years; hazard ratio [HR] 0·45, 95% CI 0·34–0·60, p<0·0001), and those achieving hsCRP less than 2 mg/L a 62% reduction (event rate 0·42 per 100 person-years; HR 0·38, 95% CI 0·26–0·56, p<0·0001). Although LDL cholesterol and hsCRP reductions were only weakly correlated in individual patients (*r* values <0·15), we recorded a 65% reduction in vascular events in participants allocated to rosuvastatin who achieved both LDL cholesterol less than 1·8 mmol/L and hsCRP less than 2 mg/L (event rate 0·38 per 100 person-years; adjusted HR 0·35, 95% CI 0·23–0·54), versus a 33% reduction in those who achieved one or neither target (event rate 0·74 per 100 person-years; HR 0·67, 95% CI 0·52–0·87) (p across treatment groups <0·0001). In participants who achieved LDL cholesterol less than 1·8 mmol/L and hsCRP less than 1 mg/L, we noted a 79% reduction (event rate 0·24 per 100 person-years; HR 0·21, 95% CI 0·09–0·52). Achieved hsCRP concentrations were predictive of event rates irrespective of the lipid endpoint used, including the apolipoprotein B to apolipoprotein AI ratio.**

**Interpretation** **For people choosing to start pharmacological prophylaxis, reduction in both LDL cholesterol and hsCRP are indicators of successful treatment with rosuvastatin.**

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## Introduction

Present guidelines for statin therapy emphasise the need to achieve specific goals for LDL cholesterol to maximise clinical outcomes.[1,2] However, statin therapy has greatest efficacy in the presence of inflammation,[3,4] and several studies show that statins reduce the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) largely independently of LDL cholesterol.[5–8] Furthermore, in both the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT–TIMI 22)[9] and Aggrastat-to-Zocor (A to Z)[10] trials of patients with acute coronary ischaemia treated with statin therapy, the best clinical outcomes were in those who not only achieved LDL cholesterol less than 1·8 mmol/L (<70 mg/dL), but who also achieved hsCRP less than 2 mg/L. These findings are consistent with the pathophysiological understanding that atherothrombosis is a disorder of both hyperlipidaemia and inflammation[11] and that statins have anti-inflammatory and lipid-lowering properties.[12,13]

Despite the consistency of these results, whether achieving lower concentrations of hsCRP after initiation of statin therapy is associated with improved clinical outcomes, in a similar manner to that associated with achieving lower concentrations of LDL cholesterol, remains controversial. We prospectively tested this hypothesis in the large-scale JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial.[14]

## Methods

### Patients and procedures

The study population was derived from JUPITER—a randomised, double-blind, placebo-controlled trial that

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| | Placebo (N=7832) | Rosuvastatin | | | | | |
|---|---|---|---|---|---|---|---|
| | | LDL ≥1·8 mmol/L (N=2110) | LDL <1·8 mmol/L (N=5606) | hsCRP ≥2 mg/L (N=4305) | hsCRP <2 mg/L (N=3411) | hsCRP <2 mg/L+LDL <1·8 mmol/L (N=2685) | hsCRP <1 mg/L+LDL <1·8 mmol/L (N=944) |
| Age (years) | 66·0 (60·0–71·0) | 65·0 (60·0–71·0) | 66·0 (61·0–71·0) | 66·0 (61·0–71·0) | 66·0 (60·0–71·0) | 66·0 (60·0–71·0) | 65·0 (60·0–71·0) |
| Women | 2957 (37·8%) | 839 (39·8%) | 2108 (37·6%) | 1798 (41·8%) | 1149 (33·7%) | 916 (34·1%) | 276 (29·2%) |
| Body-mass index (kg/m$^2$) | 28·4 (25·3–32·0) | 27·8 (24·8–31·5) | 28·5 (25·5–32·1) | 29·0 (25·7–33·0) | 27·7 (24·9–30·9) | 27·8 (25·2–31·1) | 27·4 (24·6–30·5) |
| Blood pressure (mm Hg) | | | | | | | |
| Systolic | 134 (124–145) | 134 (124–144) | 135 (124–146) | 135 (125–146) | 134 (123–145) | 134 (124–146) | 132 (120–144) |
| Diastolic | 80 (75–87) | 80 (75–87) | 80 (75–88) | 80 (75–88) | 80 (75–87) | 80 (75–87) | 80 (74–86) |
| Current smoking | 1231 (15·7%) | 378 (17·9%) | 814 (14·5%) | 740 (17·2%) | 452 (13·3%) | 329 (12·3%) | 115 (12·2%) |
| Family history of coronary disease | 936 (12·0%) | 237 (11·3%) | 657 (11·7%) | 473 (11·0%) | 421 (12·4%) | 342 (12·8%) | 116 (12·4%) |
| Metabolic syndrome* | 3274 (42·1%) | 801 (38·3%) | 2337 (42·0%) | 1859 (43·5%) | 1279 (37·8%) | 1036 (38·8%) | 331 (36·3%) |
| hsCRP (mg/L) | 4·3 (2·8–7·1) | 4·2 (2·8–7·1) | 4·2 (2·8–6·8) | 5·4 (3·6–8·6) | 3·2 (2·4–4·7) | 3·2 (2·4–4·6) | 2·8 (2·2–4·2) |
| LDL cholesterol (mmol/L) | 2·8 (2·4–3·1) | 2·9 (2·6–3·1) | 2·7 (2·4–3·1) | 2·8 (2·4–3·1) | 2·8 (2·5–3·1) | 2·8 (2·4–3·1) | 2·8 (2·4–3·0) |
| HDL cholesterol (mmol/L) | 1·3 (1·0–1·6) | 1·3 (1·1–1·6) | 1·3 (1·0–1·5) | 1·3 (1·0–1·5) | 1·3 (1·1–1·6) | 1·3 (1·0–1·5) | 1·3 (1·0–1·6) |
| Triglycerides (mmol/L) | 1·33 (0·97–1·91) | 1·30 (0·95–1·89) | 1·34 (0·96–1·91) | 1·36 (0·99–1·92) | 1·30 (0·93–1·88) | 1·32 (0·94–1·89) | 1·29 (0·92–1·84) |
| Non-HDL cholesterol (mmol/L) | 3·5 (3·1–3·8) | 3·5 (3·2–3·9) | 3·4 (3·0–3·8) | 3·5 (3·1–3·8) | 3·4 (3·1–3·8) | 3·4 (3·0–3·8) | 3·4 (3·0–3·7) |
| Apolipoprotein B (g/L) | 1·09 (0·96–1·22) | 1·13 (1·00–1·27) | 1·07 (0·94–1·20) | 1·09 (0·95–1·22) | 1·09 (0·95–1·22) | 1·07 (0·94–1·21) | 1·08 (0·94–1·20) |
| Apolipoprotein B to apolipoprotein AI ratio | 0·7 (0·6–0·8) | 0·7 (0·6–0·8) | 0·7 (0·6–0·8) | 0·7 (0·5–0·8) | 0·7 (0·5–0·8) | 0·7 (0·5–0·8) | 0·7 (0·5–0·8) |
| Glucose (mmol/L) | 5·22 (4·88–5·66) | 5·16 (4·77–5·55) | 5·22 (4·88–5·66) | 5·22 (4·83–5·66) | 5·22 (4·88–5·66) | 5·22 (4·88–5·66) | 5·22 (4·88–5·61) |
| $HbA_{1c}$ (%) | 5·7% (5·5–5·9) | 5·7% (5·5–5·9) | 5·7% (5·4–5·9) | 5·7% (5·5–6·0) | 5·7% (5·4–5·9) | 5·7% (5·4–5·9) | 5·6% (5·4–5·9) |

Data are median (IQR) or number (%). hsCRP=high-sensitivity C-reactive protein. $HbA_{1c}$=haemoglobin $A_{1c}$. *Metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.[15]

***Table 1:*** **Baseline clinical characteristics of the study population in the placebo and rosuvastatin groups according to achieved concentrations of LDL cholesterol and high-sensitivity C-reactive protein (hsCRP)**

was designed to investigate whether rosuvastatin 20 mg daily decreased the rate of first cardiovascular events compared with placebo in apparently healthy men and women with LDL cholesterol less than 3·37 mmol/L (<130 mg/dL) who are at increased vascular risk due to hsCRP concentration of 2 mg/L or more. Full details of the trial protocol and procedures have been previously presented.[14] The prespecified primary endpoint of non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularisation, or cardiovascular death was used for all analyses contained in this study.

| | Events/ patients | Event rate* | $HR^{Age}$ (95% CI) | $HR^{Age,LDL,CRP}$ (95% CI) | $HR^{Fully\ adjusted}$ (95% CI)† |
|---|---|---|---|---|---|
| **Target concentration** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| LDLC ≥1·8 mmol/L | 39/2110 | 0·91 | 0·89 (0·63–1·25) | 0·89 (0·63–1·26) | 0·85 (0·60–1·21) |
| LDLC <1·8 mmol/L | 64/5606 | 0·51 | 0·45 (0·34–0·60) | 0·46 (0·35–0·61) | 0·45 (0·33–0·59) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |
| **Percentage reduction** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| LDLC reduction <50% | 65/4181 | 0·74 | 0·70 (0·53–0·93) | 0·70 (0·53–0·93) | 0·66 (0·50–0·88) |
| LDLC reduction ≥50% | 38/3535 | 0·47 | 0·41 (0·29–0·59) | 0·42 (0·30–0·59) | 0·42 (0·29–0·59) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |

HR=hazard ratio. Data include all events occurring after randomisation. *Event rates are per 100 person-years. †Fully adjusted model controlled for age, baseline LDL cholesterol, baseline high-sensitivity C-reactive protein (hsCRP), baseline HDL cholesterol, blood pressure, sex, body-mass index, smoking status, and parental history of premature coronary heart disease.

***Table 2:*** **Hazard ratios for incident cardiovascular events in the JUPITER trial according to magnitude of reduction in LDL cholesterol (LDLC) in participants allocated to rosuvastatin**

To assess the effect of reductions in hsCRP and LDL cholesterol on trial event rates, on an a priori basis, and as part of the study protocol, concentrations of hsCRP and LDL cholesterol were obtained at randomisation and every year thereafter. For this analysis, we used baseline and 1-year values for hsCRP and LDL concentrations, which were available for 15 548 trial participants (87% of the full JUPITER cohort). Since statins maximally reduce LDL cholesterol and hsCRP within 6 weeks, we decided a priori to include all events arising after randomisation in our primary analyses instead of arbitrarily limiting the analysis to events that occurred after any specific timepoint. This approach is conservative since any misclassification of on-treatment concentrations of LDL cholesterol or hsCRP on this basis would, if anything, bias the analysis towards a null result. To test the validity of these assumptions, we also undertook secondary analyses limited only to events that occurred after the first year of treatment.

## Statistical analysis

We used Spearman correlation coefficients to assess the relation between concentrations of on-treatment LDL cholesterol and on-treatment hsCRP, as well as the correlation between percentage change over 1 year in these two variables. Consistent with the PROVE IT–TIMI 22 and A to Z trials,[9,10] we first divided the participants given rosuvastatin into two groups on the basis of whether or not the achieved LDL cholesterol concentration was 1·8 mmol/L or more, or less than this value, and used Cox proportional-hazards models to estimate relative hazards for cardiovascular events in these two groups, compared with participants allocated placebo. We also divided the participants given rosuvastatin into two groups on the basis of whether or not the achieved hsCRP concentration was greater than 2 mg/L, or less than this value, and used Cox proportional-hazards models to estimate relative hazards for cardiovascular events in these two groups, compared with those allocated placebo. As an internal check to ensure the validity of this a-priori approach, we repeated the above process dividing the cohort on the basis of achieving reductions in LDL cholesterol of greater than or less than 50%, and on the basis of achieving reductions in hsCRP of greater than or less than 50%.

To address the effect of the achieved hsCRP concentrations across the strata of achieved LDL cholesterol values, we further repeated this process after dividing the cohort given rosuvastatin into four groups on the basis of LDL cholesterol cutoff of 1·8 mmol/L, and hsCRP cutoff of 2 mg/L. We did a test for trend in event rates across these groups by assigning a score of 0 to the placebo group, a score of 1 to those in the rosuvastatin group who achieved neither target (LDL cholesterol ≥1·8 mmol/L, CRP ≥2 mg/L), a score of 2 to those in the rosuvastatin group who achieved one target (LDL cholesterol ≥1·8 mmol/L, CRP <2 mg/L; or LDL cholesterol <1·8 mmol/L, CRP ≥2 mg/L), and a score of 3 to those in the rosuvastatin group who achieved both targets (LDL cholesterol <1·8 mmol/L, CRP <2 mg/L). For ease of clinical application, we undertook similar analyses after dividing the participants given rosuvastatin into two groups: those who achieved LDL cholesterol less than 1·8 mmol/L and CRP less than 2 mg/L, and those who did not achieve one or both of these targets. We also compared outcomes for participants achieving or not achieving each of the above LDL cholesterol and hsCRP targets, restricting the analysis to those allocated to active rosuvastatin treatment. Since previous retrospective analyses[9,10] raised the hypothesis of greatest benefits in people who not only achieved LDL cholesterol less that 1·8 mmol/L, but who also achieved hsCRP concentrations less than 1 mg/L, we also undertook analyses with these alternative predetermined targets.

To address whether alternative lipid measures might affect results, we repeated all analyses substituting non-HDL cholesterol, apolipoprotein B, or the ratio of apolipoprotein B to apolipoprotein AI for LDL cholesterol. Further sensitivity analyses were done by varying target lipid concentrations.

This trial is registered with ClinicalTrials.gov, number NCT00239681.

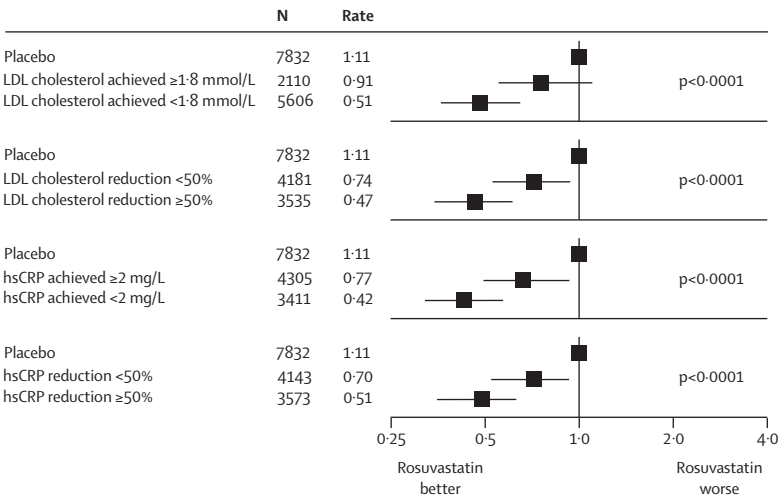


***Figure 1:*** **Hazard ratios for incident cardiovascular events in JUPITER according to achieved concentrations of LDL cholesterol or high-sensitivity C-reactive protein (hsCRP) after initiation of rosuvastatin**
Data are adjusted for age, baseline LDL and HDL cholesterol, baseline hsCRP, blood pressure, sex, body-mass index, smoking status, and parental history of premature coronary heart disease. Event rates are per 100 person-years.

| | Events/ patients | Event rate* | $HR^{Age}$ (95% CI) | $HR^{Age,LDL,CRP}$ (95% CI) | $HR^{Fully\ adjusted}$ (95% CI)† |
|---|---|---|---|---|---|
| **Target concentration** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| hsCRP ≥2 mg/L | 72/4305 | 0·77 | 0·69 (0·53–0·91) | 0·69 (0·53–0·90) | 0·68 (0·51–0·89) |
| hsCRP <2 mg/L | 31/3411 | 0·42 | 0·38 (0·26–0·56) | 0·38 (0·26–0·56) | 0·36 (0·24–0·54) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |
| **Percentage reduction** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| hsCRP reduction <50% | 63/4143 | 0·70 | 0·64 (0·48–0·85) | 0·64 (0·48–0·85) | 0·63 (0·47–0·84) |
| hsCRP reduction ≥50% | 40/3573 | 0·51 | 0·46 (0·33–0·65) | 0·46 (0·33–0·65) | 0·44 (0·31–0·62) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |

HR=hazard ratio. Data include all events occurring after randomisation. *Event rates are per 100 person-years. †Fully adjusted model controlled for age, baseline LDL cholesterol, baseline hsCRP, baseline HDL cholesterol, blood pressure, sex, body-mass index, smoking status, and parental history of premature coronary heart disease.

***Table 3:*** **Hazard ratios for incident cardiovascular events in the JUPITER trial according to magnitude of reduction in high-sensitivity C-reactive protein (hsCRP) in participants allocated to rosuvastatin**

## Role of the funding source

JUPITER was an investigator-initiated trial. The sponsor of the study collected the trial data and monitored the study sites, but had no role in the conduct of the analyses or drafting of the report. All statistical analyses were done by the investigators and the academic study statistician

| | Events/ patients | Event rate* | HR$^{Age}$ (95% CI) | HR$^{Age,LDL,CRP}$ (95% CI) | HR$^{Fully\ adjusted}$ (95% CI)† |
|---|---|---|---|---|---|
| **hsCRP cutoff <2 mg/L** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| LDL cholesterol ≥1·8 mmol/L, hsCRP ≥2 mg/L | 31/1384 | 1·11 | 1·06 (0·72–1·55) | 1·07 (0·73–1·56) | 1·06 (0·72–1·55) |
| LDL cholesterol >1·8 mmol/L, hsCRP < 2 mg/L | 8/726 | 0·54 | 0·54 (0·27–1·10) | 0·56 (0·28–1·14) | 0·42 (0·18–0·94) |
| LDL cholesterol <1·8 mmol/L, hsCRP ≥2 mg/L | 41/2921 | 0·62 | 0·55 (0·39–0·77) | 0·54 (0·39–0·76) | 0·53 (0·38–0·74) |
| LDL cholesterol <1·8 mmol/L, hsCRP <2 mg/L | 23/2685 | 0·38 | 0·35 (0·23–0·54) | 0·36 (0·23–0·55) | 0·35 (0·23–0·54) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |
| Rosuvastatin | | | | | |
| LDL cholesterol ≥1·8 mmol/L or hsCRP ≥2 mg/L | 80/5031 | 0·74 | 0·67 (0·52–0·87) | 0·67 (0·52–0·87) | 0·64 (0·49–0·84) |
| LDL cholesterol <1·8 mmol/L and hsCRP <2 mg/L | 23/2685 | 0·38 | 0·35 (0·23–0·54) | 0·36 (0·23–0·55) | 0·35 (0·23–0·54) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |
| **hsCRP cutoff <1 mg/L** | | | | | |
| Placebo | 189/7832 | 1·11 | 1·00 | 1·00 | 1·00 |
| Rosuvastatin | | | | | |
| LDL cholesterol ≥1·8 mmol/L, hsCRP ≥1 mg/L | 36/1874 | 0·95 | 0·91 (0·64–1·30) | 0·93 (0·65–1·33) | 0·89 (0·62–1·28) |
| LDL cholesterol ≥1·8 mmol/L, hsCRP <1 mg/L | 3/236 | 0·64 | 0·65 (0·21–2·03) | 0·67 (0·21–2·10) | 0·46 (0·11–1·85) |
| LDL cholesterol <1·8 mmol/L, hsCRP ≥1 mg/L | 59/4662 | 0·56 | 0·50 (0·38–0·67) | 0·50 (0·38–0·67) | 0·49 (0·37–0·66) |
| LDL cholesterol <1·8 mmol/L, hsCRP <1 mg/L | 5/944 | 0·24 | 0·21 (0·09–0·52) | 0·22 (0·09–0·54) | 0·21 (0·09–0·51) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |
| Rosuvastatin | | | | | |
| LDL cholesterol ≥1·8 mmol/L or hsCRP ≥1 mg/L | 98/6772 | 0·67 | 0·61 (0·48–0·77) | 0·61 (0·48–0·78) | 0·59 (0·46–0·75) |
| LDL cholesterol <1·8 mmol/L and hsCRP <1 mg/L | 5/944 | 0·24 | 0·21 (0·09–0·52) | 0·22 (0·09–0·54) | 0·21 (0·09–0·51) |
| p value | | | <0·0001 | <0·0001 | <0·0001 |

HR=hazard ratio. Data include all events occurring after randomisation.*Event rates are per 100 person-years. †Fully adjusted model controlled for age, baseline LDL cholesterol, baseline hsCRP, baseline HDL cholesterol, blood pressure, sex, body-mass index, smoking status, and parental history of premature coronary heart disease.

***Table 4:*** **Hazard ratios for incident cardiovascular events in the JUPITER trial in the placebo group and according to achieved concentrations of both LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) in participants allocated to rosuvastatin**

(RJG). PMR and RJG had full access to all study data and had final responsibility for the decision to submit for publication.

## Results

Table 1 shows baseline characteristics of the study population in the placebo and rosuvastatin groups according to achieved LDL cholesterol and achieved hsCRP concentrations. Baseline age, blood pressure, HDL cholesterol, triglycerides, glucose, and haemoglobin $A_{1c}$ were much the same between groups (table 1).

As expected, baseline LDL cholesterol values were lower in particpants given rosuvastatin who subsequently achieved LDL cholesterol less than 1·8 mmol/L compared with those who did not; similarly baseline hsCRP concentrations were lower in those given rosuvastatin who achieved hsCRP less than 2 mg/L (table 1). Participants achieving lower LDL cholesterol and hsCRP concentrations on rosuvastatin were less likely to be women or to smoke, had lower body-mass index, and were more likely to have a family history of coronary disease (table 1). All these potential confounding factors, as well as baseline HDL cholesterol and blood pressure, were included in the fully adjusted models. By contrast, in participants allocated to placebo, only 106 (1%) achieved the targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 2 mg/L, and 29 (<1%) achieved the targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 1 mg/L, largely because of off-trial statin use.

Rosuvastatin reduced the median LDL cholesterol by 50% (p<0·0001) and the median hsCRP by 37% compared with placebo (p<0·0001). However, the magnitude of correlation between achieved LDL cholesterol and achieved hsCRP in participants given rosuvastatin was small ($r$=0·10), so that less than 2% of the variance in achieved hsCRP was explained by the variance in achieved LDL cholesterol. The correlations between achieved hsCRP and achieved apolipoprotein B ($r$=0·10), between achieved hsCRP and the achieved ratio of apolipoprotein B to apolipoprotein AI ($r$=0·16), and between the percentage reduction in hsCRP and the percentage reduction in LDL cholesterol ($r$=0·15) were also small.

As previously reported,[14] rosuvastatin allocation resulted in a 44% reduction in the trial primary endpoint (HR 0·56, 95% CI 0·46–0·69, p<0·0001). We detected no evidence of a significant interaction between the overall efficacy of rosuvastatin and baseline concentrations of hsCRP less than 5 mg/L (HR 0·49, 95% CI 0·37–0·65) or 5 mg/L or greater (0·66, 0·49–0·89; p for interaction=0·15), or baseline LDL cholesterol less than 2·6 mmol/L (0·66, 0·47–0·92) or 2·6 mmol/L or more (0·52, 0·40–0·67; p for interaction=0·28). However, as expected, the magnitude of reduction in LDL cholesterol with rosuvastatin was directly related to the magnitude of clinical benefit. Compared with placebo, participants allocated to rosuvastatin who did not achieve LDL cholesterol less than 1·8 mmol/L had no significant reduction in vascular events (HR 0·89, 95% CI 0·63–1·25, p=0·49), whereas we recorded a 55% reduction in those who did achieve this target (0·45, 0·34–0·60, p<0·0001) (p for trend across LDL cholesterol strata <0·0001, p for comparison between active treatment groups=0·001). These effects were minimally changed after adjustment for baseline LDL cholesterol or for any of the other risk factors at study entry (table 2). We recorded a similar relation between on-treatment LDL cholesterol and event rates in analyses stratified by percentage reduction (table 2, figure 1).

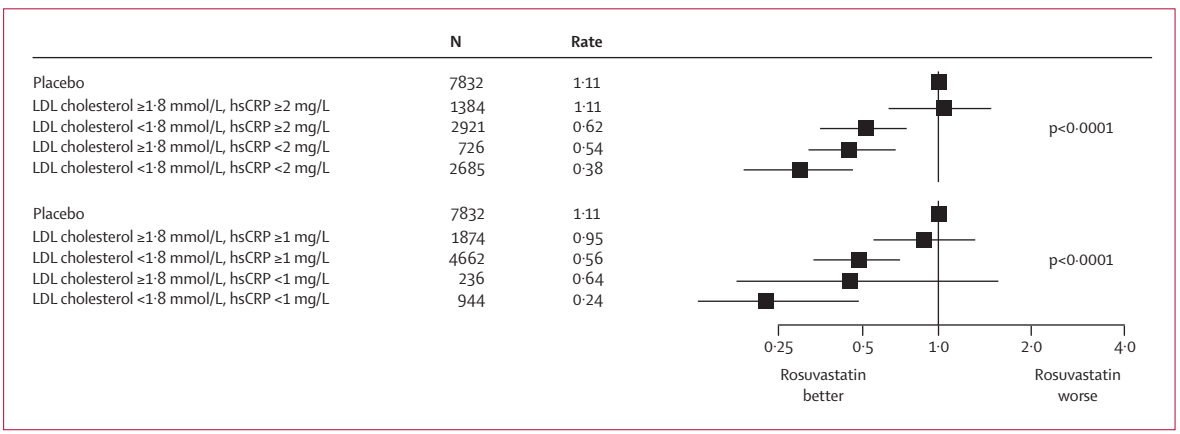


***Figure 2:*** **Hazard ratios for incident cardiovascular events in JUPITER according to achieved concentrations of LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) after initiation of rosuvastatin**

Data are adjusted for age, baseline LDL and HDL cholesterol, baseline hsCRP, blood pressure, sex, body-mass index, smoking status, and parental history of premature coronary heart disease. Event rates are per 100 person-years.

Despite little correlation between reductions in LDL cholesterol and hsCRP, the magnitude of decrease in hsCRP was directly related to the magnitude of clinical benefit. Compared with placebo, participants allocated to rosuvastatin who did not achieve hsCRP less than 2 mg/L had a 31% decrease in events (HR 0·69, 95% CI 0·53–0·91, p=0·007), whereas we noted a 62% reduction in those who did achieve this hsCRP target (0·38, 0·26–0·56, p<0·0001) (p for trend across hsCRP strata <0·0001, p for comparison between active treatment groups=0·007). These effects were minimally changed after adjustment for baseline hsCRP or for any of the other risk factors at baseline (table 3). We recorded a similar relation between on-treatment hsCRP and event rates in analyses stratified by percentage reduction (table 3, figure 1).

We detected the lowest risk of cardiovascular events in participants given rosuvastatin who not only achieved low concentrations of LDL cholesterol, but who also achieved low values of hsCRP (table 4 and figure 2). In similar analyses restricted to participants who achieved LDL cholesterol concentrations less than 1·8 mmol/L, participants who achieved hsCRP concentrations less than 2 mg/L had better clinical outcomes than did those who did not (table 4).

Figure 3A shows the cumulative incidence of cardiovascular events in the placebo and rosuvastatin groups, according to whether or not the targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 2 mg/L were achieved. In fully adjusted analyses, the hazard ratio was 0·64 (95% CI 0·49–0·84) for one or both targets not achieved, and 0.35 (0·23–0·54) for both targets achieved (p for trend across groups <0·0001, p for comparison between active treatment groups 0·033).

We recorded a 79% reduction in hazard in participants who achieved the targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 1 mg/L (table 4, figure 2). In similar analyses restricted to participants who achieved LDL cholesterol concentrations less than 1·8 mmol/L, those who achieved hsCRP concentrations less than 1 mg/L had better clinical outcomes than did those who did not.

Figure 3B shows the cumulative incidence of cardiovascular events in the placebo and rosuvastatin groups, according to whether or not the targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 1 mg/L were achieved. In fully adjusted analyses, the hazard ratio was 0·59 (95% CI 0·46–0·75) for one or both targets not achieved, and 0·21 (0·09–0·51) for both targets achieved (p for trend across groups <0·0001, p for comparison between active treatment groups=0·037).

We did several additional analyses to address the robustness of these findings. First, although our primary a-priori analyses were based on all events after randomisation with achieved concentrations of LDL cholesterol and hsCRP available, we repeated these analyses limiting the data to events occurring after the 1-year blood samples were obtained, and noted a very similar pattern of results (webappendix p 1).

See Online for webappendix

Second, because others have postulated that non-HDL cholesterol, apolipoprotein B, or the ratio of apolipoprotein B to apolipoprotein AI might be better than LDL cholesterol for monitoring of statin therapy,[16,17] we repeated these analyses substituting each of these alternative lipid measures for LDL cholesterol. For these analyses, we used a non-HDL cholesterol target of less than 2·6 mmol/L, an apolipoprotein B target of less than 0·8 g/L, and a target ratio of apolipoprotein B to apolipoprotein AI of less than 0·5, since the proportions of participants above and below these cutoffs were similar to that above or below the target of LDL cholesterol less than 1·8 mmol/L. In all these analyses, participants achieving low concentrations of hsCRP and low values of the alternative lipid variable had better

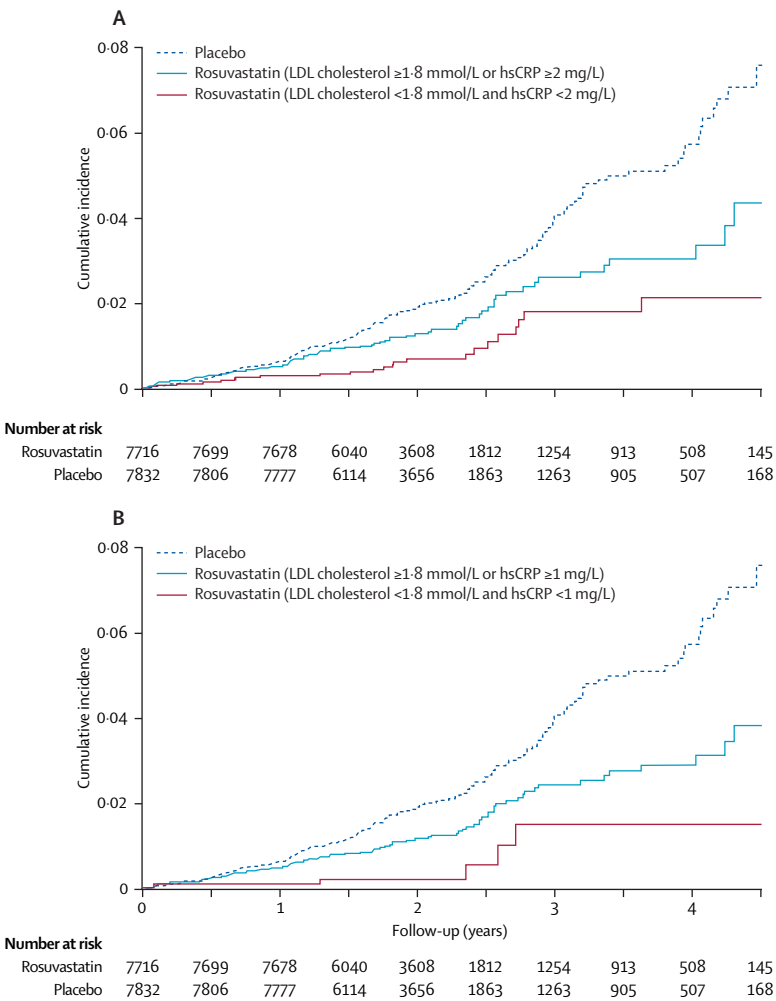


*Figure 3:* **Cumulative incidence of cardiovascular events in JUPITER in the placebo and rosuvastatin groups according to whether or not reductions in both LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) were achieved**

(A) Analysis using targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 2 mg/L. (B) Analysis using targets of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 1 mg/L.

clinical outcomes than did those who did not achieve the respective targets (all p values for trend across groups <0·001, all p values for comparisons between active treatment groups <0·05 apart from apolipoprotein B, for which p=0·057) (figure 4). Further, irrespective of the alternative lipid measure used, we detected a similar pattern of risk reduction associated with achieved hsCRP across strata of achieved lipid concentrations (webappendix p 2).

Finally, to address whether the use of alternative lipid cutoffs might affect our findings, we repeated the above analyses with an LDL cholesterol target of less than 1·4 mmol/L (<55 mg/dL) (the median on-treatment LDL cholesterol concentrations within JUPITER) rather than the clinical target of LDL cholesterol less than 1·8 mmol/L. In this sensitivity analysis, participants who achieved the targets of LDL cholesterol less than 1·4 mmol/L and hsCRP less than 2 mg/L had better clinical outcomes than did those who did not (data not shown). We recorded similar findings in sensitivity analyses that used the median on-treatment cutoffs observed within the trial for non-HDL cholesterol (<2·0 mmol/L), apolipoprotein B (<0·66 g/L), or the ratio of apolipoprotein B to apolipoprotein AI (<0·4) (data not shown).

## Discussion

In healthy men and women starting rosuvastatin therapy in the JUPITER trial, achievement of target concentrations of LDL cholesterol less than 1·8 mmol/L and hsCRP less than 2 mg/L was associated with improved event-free survival compared with achievement of neither target or with achievement of reduced LDL cholesterol alone. The differential outcomes that we recorded on the basis of achieved concentrations of LDL cholesterol and hsCRP remained significant and unchanged in magnitude after adjustment for all available baseline characteristics that varied between groups, including concentrations of both LDL cholesterol and hsCRP before randomisation. We detected similar effects in analogous assessments when non-HDL cholesterol, apolipoprotein B, or the ratio of apolipoprotein B to apolipoprotein AI were substituted for LDL cholesterol, and in sensitivity analyses based on even more aggressive lipid targets. We noted the greatest hazard reduction in participants who achieved LDL cholesterol concentrations less than 1·8 mmol/L and hsCRP concentrations less than 1 mg/L.

We believe these findings to be of interest for several reasons. First, these prospective data in an outpatient prevention setting lend support to controversial data from the PROVE IT–TIMI 22[9] and A to Z[10] trials in which patients with acute coronary syndrome who achieved hsCRP concentrations less than 2 mg/L and LDL cholesterol concentrations less than 1·8 mmol/L had the best clinical outcomes for patients being treated with statin therapy. The JUPITER design allowed us to simultaneously adjust for a wide range of baseline clinical characteristics, including entry values of LDL cholesterol and hsCRP. Thus, we can conclude that the differences in clinical outcome result from drug response rather than from difference in baseline clinical characteristics.

Second, data from this study derive from a population of healthy men and women and are thus free of potential confounding effects that might have accrued in the PROVE IT–TIMI 22 and A to Z studies in which on-treatment hsCRP and LDL cholesterol concentrations were ascertained after an acute ischaemic event. The present data are also consistent with intravascular ultrasound evidence from the REVERSAL trial[18] of patients with stable coronary artery disease, in which

plaque regression after statin therapy was detected only when both hsCRP and LDL cholesterol were reduced.

Third, these data could provide insight into mechanisms by which statin therapy reduces vascular risk. In addition to being highly effective agents to reduce cholesterol through inhibition of the hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase pathway, statins reduce inflammatory cell adhesion and monocyte recruitment to endothelial cells, change smooth muscle migration in developing plaques, and favourably affect matrix metalloproteinases leading to plaque stabilisation.[12,13] The extent to which these anti-inflammatory properties affect clinical outcomes, and whether or not these effects are independent of LDL cholesterol, remains an intense area of research.[19] Nonetheless, our previous work with pravastatin,[5,6,9] lovastatin,[4] cerivastatin,[7] simvastatin,[8,10] atorvastatin,[9] and now rosuvastatin has consistently shown that more efficacious statins have a greater effect on inflammation, and that for any given statin, hsCRP response varies with dose. We chose to use rosuvastatin 20 mg when designing JUPITER since a core scientific goal was to assess the use of robust LDL cholesterol and hsCRP reduction in a population of patients who did not qualify for statin therapy according to conventional guidelines, but who were at increased vascular risk because of an enhanced inflammatory profile. Thus, the finding that clinical benefits are maximised when both LDL cholesterol and hsCRP are reduced provides new insight into why more potent statins (as tested in the PROVE IT–TIMI 22 trial)[20] or higher doses of the same statin (as tested in the Treating to New Targets trial)[21] result in increased clinical benefits.

Limitations of our data merit consideration. Although our data derive from a large randomised trial, analyses according to achieved LDL cholesterol and achieved hsCRP are no longer randomised; thus, although we adjusted for all available clinical characteristics between study groups, residual confounding cannot be fully excluded. However, our targets for achieved LDL cholesterol and achieved hsCRP were prespecified on the basis of previous published work and are not derived from data. Long-term safety data for rosuvastatin are scarce in our trial because the median exposure is 1·9 years (maximum 5 years). Finally, although restriction of the range of both LDL cholesterol and hsCRP by design in our study could in theory limit generalisation, these same features greatly reduce the potential for baseline confounding and thus enhance validity. Moreover, our data are consistent with those from the AFCAPS/TexCAPS[4] trial that had a much wider range of concentrations of LDL cholesterol and hsCRP at baseline, and with those from the aforementioned PROVE IT–TIMI 22,[9] A to Z,[10] and REVERSAL[18] trials that studied patients with overt hyperlipidaemia.

Despite the pathophysiological evidence presented here, in low-risk primary prevention populations with raised LDL cholesterol or hsCRP, initial interventions should remain lifestyle recommendations for dietary restriction, exercise, and smoking cessation. However, as our findings have shown, for people choosing to start pharmacological prophylaxis, reductions in both LDL cholesterol and hsCRP are indicators of the success of treatment with statin therapy.[9,10,22]

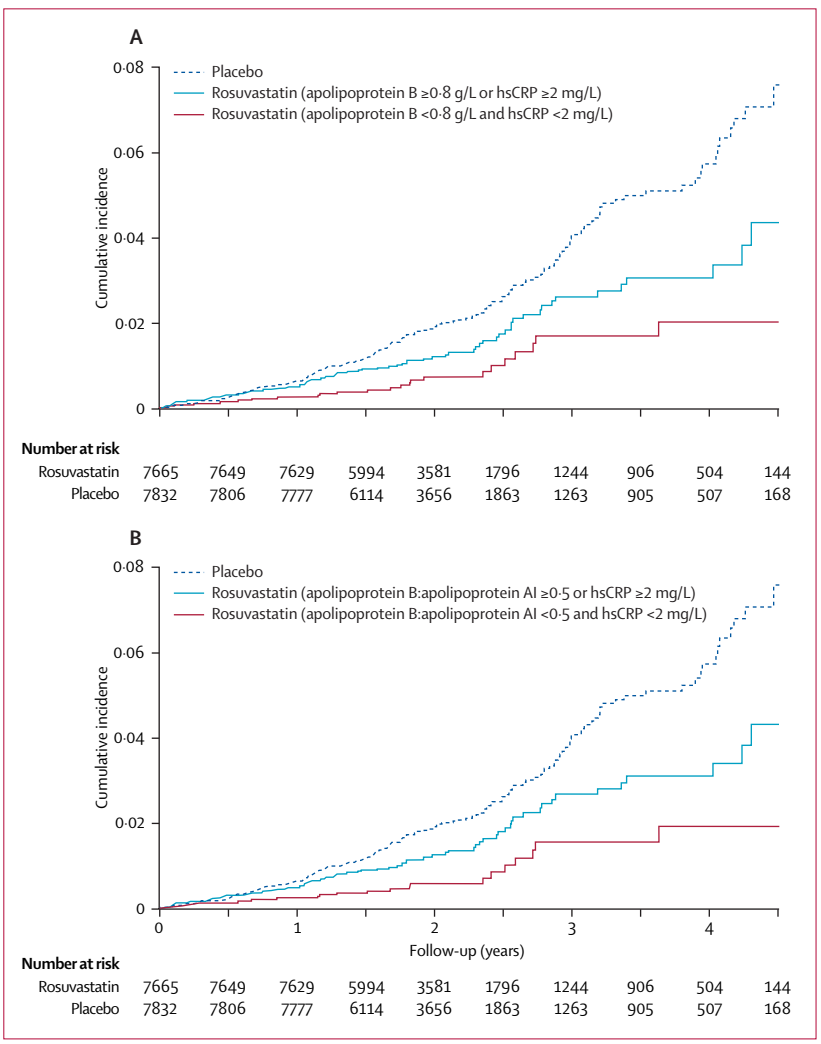


***Figure 4:*** **Cumulative incidence of cardiovascular events in JUPITER in the placebo and rosuvastatin groups according to whether or not reductions in alternative lipid concentrations and high-sensitivity C-reactive protein (hsCRP) were achieved**

(A) Analysis using targets of apolipoprotein B less than 0·8 g/L and hsCRP less than 2 mg/L. (B) Analysis using targets of ratio of apolipoprotein B to apolipoprotein AI less than 0·5 and hsCRP less than 2 mg/L.

**Contributors**

PMR, the Principal Investigator and Trial Chairman of JUPITER, designed and undertook the trial, interpreted the data, and wrote this report. RJG, the academic study statistician, along with ED and JGM, managed the dataset and undertook the independent statistical analyses. FAHF, JG, AMG, JJPK, WK, PL, AJL, BGN, JS, and JTW are members of the JUPITER Steering Committee and assisted in multiple phases of the trial including participant recruitment, data collection, and data interpretation. All authors have seen and approved the final version of the report.

### Conflict of interest statement

During the period of this study, PMR reports having received investigator-initiated research grant support from the National Heart Lung and Blood Institute, the National Cancer Institute, the Donald W Reynolds Foundation, the Leducq Foundation, AstraZeneca, Novartis, Merck, Abbott, Roche, and Sanofi-Aventis; consulting fees and/or lecture fees from AstraZeneca, Novartis, Merck-Schering Plough, Sanofi-Aventis, ISIS, and Vascular Biogenics; and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. These patents have been licensed to several entities, including AstraZeneca. FAHF reports having received research grants, lecture fees, and consulting fees from AstraZeneca, Pfizer, Schering-Plough, Sanofi-Aventis, and Merck. JG reports having received lecture fees from AstraZeneca, Schering Plough, Pfizer, Novartis, and Sanofi-Aventis; and consulting fees from AstraZeneca, Merck, Schering-Plough, Pfizer, Novartis, and Sanofi-Aventis. AMG reports having received consulting fees from Dupont, Novartis, Aegerion, Arisaph, KOWA, Merck, Merck Schering Plough, Pfizer, and Reliant. JJPK reports receiving research grant support from AstraZeneca, Pfizer, Roche, Novartis, Merck, Merck Schering Plough, ISIS, Genzyme, and Sanofi-Aventis; lecture fees from AstraZeneca, GlaxoSmithKline, Pfizer, Novartis, and Boehringer-Ingelhiem; and consulting fees from AstraZeneca, Abbott, Pfizer, ISIS, Genzyme, Roche, Novartis, Merck, Merck Schering Plough, and Sanofi-Aventis. WK reports receiving research grant support from Dade-Behring and GlaxoSmithKline; lecture fees from AstraZeneca, Pfizer, Novartis, GlaxoSmithKline, and Boehringer-Ingelheim; and consulting fees from GlaxoSmithKline and Roche. PL reports consulting fees from and serves on the Scientific Advisory boards of VIA Pharmaceutical, Interleukin Genetics, Bind Biosciences, Carolus Therapeutics, and Kowa Research Institute. AJL reports receiving research grant support, lecture fees, and consulting fees from AstraZeneca, Takeda, and Novartis. BGN reports receiving lecture fees from AstraZeneca, Sanofi-Aventis, Pfizer, Boehinger Ingelheim, and Merck; and consulting fees from AstraZeneca, Abbott, and BG Medicine. JS reports receiving lecture fees from AstraZeneca, Pfizer, and Merck; and consulting fees from AstraZeneca, Merck, Pfizer, Nicox, and Oxford Biosciences. RJG reports receiving research grant support from AstraZeneca and Bristol Myers Squibb. JTW, ED, and JGMF declare that they have no conflict of interest.

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