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Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation risk \(\geq 5\%\) or Framingham risk \(>20\%\): post hoc analyses of the JUPITER trial requested by European health authorities

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**Aims**

On the basis of the JUPITER trial, European health authorities recently approved the use of rosuvastatin to reduce first major cardiovascular events among ‘high’ global risk primary prevention patients defined either by Framingham risk score \(>20\%\) or European systematic coronary risk evaluation (SCORE) \(\geq 5\%\). However, as these are post hoc analyses, data describing these subgroups have not previously been available to the clinical community.

**Methods and results**

We randomized 17 802 apparently healthy men aged \(\geq 50\) and women \(\geq 60\) with low-density lipoprotein cholesterol (LDL-C) \(<3.4\) mmol/L, who were at an increased vascular risk due to elevated levels of C-reactive protein measured with a high-sensitivity (hs) assay to rosuvastatin 20 mg daily or placebo. Patients with high global cardiovascular risk at baseline were identified by 10-year Framingham risk score \(>20\%\) or SCORE risk \(\geq 5\%\). During 1.8-year median follow-up (maximum 5 years) of patients with Framingham risk \(>20\%\), the rate of myocardial infarction/stroke/cardiovascular death was 9.4 and 18.2 per 1000 person-years in rosuvastatin and placebo-allocated patients, respectively \([\text{hazard ratio (HR): } 0.50, 95\% \text{ confidence interval (CI): } 0.27–0.93, P = 0.028]\). Among patients with SCORE risk \(\geq 5\%\), the corresponding rates were 6.9 and 12.0 using a model extrapolating risk for age \(\geq 65\) years \([\text{HR: } 0.57, 95\% \text{ CI: } 0.43–0.78, P = 0.0003]\) and rates were 5.9 and 12.7 when risk for age was capped at 65 years \([\text{HR: } 0.47, 95\% \text{ CI: } 0.32–0.68, P < 0.0001]\).

**Conclusion**

In primary prevention patients with elevated hs C-reactive protein who have high global cardiovascular risk (10-year Framingham risk score \(>20\%\) or SCORE risk \(\geq 5\%\)), but LDL-C levels not requiring pharmacologic treatment, rosuvastatin 20 mg significantly reduced major cardiovascular events.

ClinicalTrial.gov Identifier: NCT00239681

**Keywords**

Rosuvastatin • Coronary heart disease • C-reactive protein • High risk

**Introduction**

The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to investigate whether rosuvastatin decreased first major cardiovascular events among patients with levels of low-density lipoprotein cholesterol (LDL-C) \(<3.4\) mmol/L (130 mg/dL), but who were at increased cardiovascular risk due to elevated levels of
Methods

JUPITER was a double-blind, placebo-controlled trial which randomized apparently healthy men aged ≥50 and women aged ≥60, with LDL-C <3.4 mmol/L (130 mg/dL) and C-reactive protein ≥2 mg/L in 26 countries. Participants did not qualify for statin therapy according to guidelines in effect in 2003, but were at increased cardiovascular risk due to evidence of systemic inflammation.

Full details of the trial protocol, procedures, and methods of confirming clinical endpoints and ascertaining adverse events have been presented previously. Trial exclusion criteria included use within 6 weeks before screening of any lipid-lowering therapies, the current use of rosvastatin for primary prevention of cardiovascular events among JUPITER eligible participants with elevated hs C-reactive protein and at least one additional risk factor. In contrast, the United States Food and Drug Administration approved the use of rosvastatin for primary prevention of cardiovascular events among JUPITER eligible participants with elevated hs C-reactive protein and at least one additional risk factor. In contrast, the Dutch Medical Agency (the MEB) and 18 other European health authorities have approved rosvastatin for the subgroup of trial participants who were considered to be at 'high risk' either on the basis of an estimated 10-year Framingham risk score >20% or an estimated systematic coronary risk evaluation (SCORE) risk of ≥5%. As neither of these criteria were used in the design of the JUPITER trial, these post hoc data, not published previously, are likely to be of utility for European practitioners and are thus presented here.

Results

JUPITER enrolled 17 802 men and women (6515 in Europe), and randomized 8901 each to rosvastatin 20 mg daily and placebo. At baseline, 9% of the cohort was considered to be at ‘high risk’ for a first cardiovascular event on the basis of having a 10-year Framingham risk of MI/coronary death above 20%; 52% were considered to be at ‘high risk’ on the basis of having a 10-year SCORE risk of cardiovascular death of 5% or higher using the extrapolated model, and 35% were considered to be at ‘high risk’ using the
Rosuvastatin in high-risk patients

capped SCORE model. Baseline characteristics of these high-risk patients are shown by treatment allocation (Table 1). As anticipated, when compared with the entire JUPITER cohort, the higher-risk patients were older, more often male and more likely to smoke, have hypertension and low levels of HDL-C. Differences between the high-risk Framingham and SCORE groups reflect the patient characteristics included in the risk algorithms and their weighted contribution to individuals’ estimated global cardiovascular risk. In particular, metabolic syndrome was more prevalent among high-risk Framingham patients.

For the entire JUPITER cohort, rosuvastatin lowered LDL-C by 50%, triglycerides by 17% and hs C-reactive protein by 37%, whereas it increased HDL-C by 4% compared with placebo (P < 0.001 for all from baseline to year 1).1 In the high-risk groups, effects of rosuvastatin on lipoproteins and hs C-reactive protein were similar to those seen for the entire cohort (Table 2), with significant reductions in LDL-C, triglycerides, and hs C-reactive protein (P < 0.0001 vs. placebo for all) and a significant increase in HDL-C (P < 0.0001).

At study closure (median follow-up 1.8 years; maximal follow-up 5 years), the occurrence of MI/stroke/cardiovascular death was lower among high-risk subjects allocated to rosuvastatin compared with placebo (HR: 0.50, 95% CI: 0.27–0.93 for Framingham risk score >20%; HR: 0.57, 95% CI: 0.43–0.78 for SCORE risk ≥5% extrapolated model; HR: 0.47, 95% CI: 0.32–0.68 for SCORE risk ≥5% capped model; Figure 1, Table 3). The proportional reduction in MI/stroke/cardiovascular death with rosuvastatin was similar for patients with Framingham risk score above or below 20% (P for interaction = 0.95), or SCORE risk above or below 5% (P for interaction = 0.37 capped model, 0.25 extrapolated model).

Rosuvastatin significantly reduced the occurrence of the primary composite endpoint of MI/stroke/arterial revascularization/unstable angina/coronary vascular death as well as fatal/non-fatal MI and fatal/non-fatal stroke among patients with SCORE ≥5% (in both the extrapolated and capped models; Table 3, Figure 2) and reduced all-cause mortality in the capped SCORE model (Table 3).

In the higher-risk patients, there was no evidence of heterogeneity for the endpoint of MI/stroke/cardiovascular death in subgroups by gender, age, race/ethnicity, hypertension, smoking, family history of premature coronary heart disease, baseline HDL-C, or C-reactive protein (Figure 3). Patients with body mass index >30 kg/m² at baseline appeared to benefit less from rosuvastatin treatment compared with non-obese patients, but this interaction between treatment assignment and body mass index was not observed for the JUPITER cohort as a whole and thus is likely to be more apparent than real.

In the high-risk patients, serious adverse events were reported with similar frequency in rosuvastatin and placebo-allocated patients (Table 4). A small excess of myalgia was reported with rosuvastatin in patients with Framingham risk score >20%.

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### Table 1  Baseline characteristics according to the estimated 10-year risk defined by the Framingham risk score or the systematic coronary risk evaluation risk algorithm

|                | Entire cohort | Framingham 10-year risk >20% | SCORE 10-year risk ≥5% |
|----------------|--------------|------------------------------|------------------------|
|                | Rosuvastatin | Placebo                      | Rosuvastatin           | Placebo | Rosuvastatin | Placebo |
| n              | 17 802       | 786                          | 772                    | 4619     | 4683         | 3130    | 3177    |
| Age (years)    | 66           | 74                           | 74                     | 70       | 70           | 67      | 67      |
| Female (%)     | 38           | 17                           | 15                     | 32       | 31           | 12      | 11      |
| Race or ethnic group (%) |            |                              |                        |          |              |         |
| White          | 71           | 68                           | 67                     | 72       | 72           | 74      | 74      |
| Black          | 13           | 15                           | 14                     | 14       | 14           | 14      | 14      |
| Hispanic       | 13           | 14                           | 17                     | 10       | 10           | 7       | 7       |
| Other          | 4            | 2                            | 2                      | 2        | 3            | 4       | 4       |
| Hypertension (%) | 57          | 87                           | 86                     | 67       | 67           | 69      | 68      |
| Current smoker (%) | 16         | 32                           | 31                     | 21       | 22           | 30      | 31      |
| Family history premature CHD (%) | 12         | 8                            | 11                     | 10       | 10           | 10      | 10      |
| HDL-C < 1.0 mmol/L (%) | 23        | 60                           | 60                     | 22       | 22           | 24      | 24      |
| Body mass index (kg/m²) | 28        | 28                           | 28                     | 28       | 28           | 28      | 28      |
| Metabolic syndrome (%) | 41        | 68                           | 69                     | 41       | 41           | 40      | 40      |
| Framingham 10-year risk score | 10       | 25                           | 25                     | 16       | 16           | 16      | 16      |
| SCORE 10-year risk | 5         | 14                           | 14                     | 9        | 9            | 10      | 10      |

Values are median or n (%). SCORE, systematic coronary risk evaluation; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol.

*aCHD in a male first-degree relative before age 55 or in a female first-degree relative before age 65.*

*bMetabolic syndrome defined as three or more of the following: waist circumference ≥102 cm (men) and 89 cm (women); triglycerides ≥1.7 mmol/L; HDL-C < 1.0 mmol/L (men) and 1.3 mmol/L (women); blood pressure ≥85 mmHg diastolic or 130 mmHg systolic or treated hypertension; fasting glucose ≥5.6 mmol/L.*
(rosuvastatin 5.9% and placebo 5.3%) or SCORE risk ≥5% (rosuvastatin 7.9%, placebo 6.5% for the extrapolated model; 7.4 vs. 5.8% for the capped model). Myopathy, myositis, and rhabdomyolysis were reported with similar frequency in the two treatment groups. In the entire JUPITER cohort, investigator-reported diabetes was not consistently more frequent with rosuvastatin in the higher-risk patients (HR: 0.70, 95% CI: 0.41–1.19, P = 0.19 for Framingham risk score ≥20%; HR: 1.11, 95% CI: 0.86–1.43, P = 0.43 for extrapolated SCORE risk ≥5%; HR: 0.99, 95% CI: 0.72–1.36, P = 0.95 for capped SCORE risk). At 2 years following randomization, a 0.1% greater increase in glycosylated haemoglobin was observed with rosuvastatin compared with placebo (P = 0.001 vs. placebo for the high-risk groups). However, on-treatment fasting glucose levels were similar in the two treatment groups (P = 0.95 vs. placebo for Framingham risk score ≥20%; P = 0.19 for extrapolated SCORE risk ≥5%; P = 0.52 for the capped SCORE model).

### Table 2  Lipoprotein and high-sensitivity C-reactive protein levels in high-risk subgroups

|                | Framingham 10-year risk >20% | SCORE 10-year risk >5% | Capped model |
|----------------|------------------------------|------------------------|--------------|
|                | Rosuvastatin | Placebo | Extrapolated model | Rosuvastatin | Placebo | Rosuvastatin | Placebo |
| LDL-C (mmol/L) |                |          |                    |                |          |                |          |
| Baseline       | 2.8 (2.5–3.1) | 2.8 (2.5–3.1) | 2.8 (2.5–3.1) | 2.8 (2.5–3.1) | 2.8 (2.5–3.1) | 2.8 (2.5–3.1) |
| Year 1         | 1.3 (1.1–1.9) | 2.8 (2.4–3.2) | 1.4 (1.1–1.8) | 2.8 (2.4–3.2) | 1.4 (1.1–1.9) | 2.8 (2.4–3.2) |
| % change       | -51           | 0         | -49               | +2             | -49         | +2             |
| P-value        | <0.0001       | <0.0001   | <0.0001           | <0.0001        | <0.0001     | <0.0001        |
| Non-HDL-C (mmol/L) |                |          |                    |                |          |                |          |
| Baseline       | 3.7 (3.3–4.0) | 3.7 (3.3–4.0) | 3.5 (3.1–3.87) | 3.5 (3.1–3.8) | 3.5 (3.1–3.8) | 3.5 (3.1–3.8) |
| Year 1         | 2.0 (1.7–2.6) | 3.6 (3.2–4.1) | 2.0 (1.6–2.5) | 3.5 (3.0–4.0) | 2.0 (1.7–2.5) | 3.5 (3.0–4.0) |
| % change       | -45           | 0         | -43               | +2             | -42         | +2             |
| P-value        | <0.0001       | <0.0001   | <0.0001           | <0.0001        | <0.0001     | <0.0001        |
| HDL-C (mmol/L) |                |          |                    |                |          |                |          |
| Baseline       | 1.0 (0.9–1.1) | 1.0 (0.9–1.1) | 1.3 (1.1–1.6) | 1.3 (1.1–1.6) | 1.2 (1.0–1.5) | 1.2 (1.0–1.5) |
| Year 1         | 1.1 (1.0–1.3) | 1.0 (0.9–1.2) | 1.3 (1.1–1.7) | 1.3 (1.1–1.6) | 1.3 (1.1–1.6) | 1.3 (1.1–1.6) |
| % change       | +9            | +3        | +6                | 0              | +6         | 0              |
| P-value        | <0.0001       | <0.0001   | <0.0001           | <0.0001        | <0.0001     | <0.0001        |
| Triglycerides (mmol/L) |                |          |                    |                |          |                |          |
| Baseline       | 1.7 (1.3–2.5) | 1.7 (1.2–2.5) | 1.3 (0.9–1.9) | 1.3 (0.9–1.9) | 1.3 (0.9–1.9) | 1.3 (0.9–1.9) |
| Year 1         | 1.3 (1.0–1.8) | 1.6 (1.2–2.4) | 1.1 (0.8–1.5) | 1.3 (1.0–1.8) | 1.1 (0.8–1.6) | 1.3 (1.0–1.9) |
| % change       | -22           | -3        | -16               | 0              | -16        | 1              |
| P-value        | <0.0001       | <0.0001   | <0.0001           | <0.0001        | <0.0001     | <0.0001        |
| hs C-reactive protein (mg/L) |                |          |                    |                |          |                |          |
| Baseline       | 4.6 (3.0–7.9) | 4.6 (3.1–7.8) | 4.2 (2.9–7.1) | 4.4 (2.9–7.3) | 4.2 (2.8–6.9) | 4.4 (2.9–7.2) |
| Year 1         | 2.5 (1.3–4.8) | 3.7 (2.3–6.7) | 2.3 (1.3–4.6) | 3.6 (2.0–6.4) | 2.2 (1.2–4.5) | 3.5 (2.0–6.4) |
| % change       | -49           | -17       | -46               | -21            | -46        | -21            |
| P-value        | <0.0001       | <0.0001   | <0.0001           | <0.0001        | <0.0001     | <0.0001        |

Values are median (interquartile range) or median (%); SCORE, systematic coronary risk evaluation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs C-reactive protein.}

### Discussion

JUPITER investigated the effect of rosuvastatin 20 mg daily compared with placebo on major cardiovascular events in a population not requiring treatment under guidelines in effect in 2003, but at an increased cardiovascular risk on the basis of age and elevated hs C-reactive protein. To provide European practitioners access to post hoc subgroup data that were influential to the European health authorities, in this analysis, we limited the target population to select an even higher risk group using two global risk assessment algorithms, Framingham and SCORE. In these higher risk subgroups, rosuvastatin lowered LDL-C, triglycerides, and hs C-reactive protein and raised HDL-C, consistent with effects observed for the entire cohort. Rosuvastatin reduced the risk of the composite endpoint of MI/stroke/cardiovascular death by 50% in the high-risk Framingham group (P = 0.028 vs. placebo), 43% in the high-risk SCORE group using the extrapolated model (P = 0.0003) and 53% (P < 0.0001) using the capped model, consistent with the 47% reduction observed for the entire cohort.
Figure 1 Cumulative incidence of myocardial infarction/stroke/cardiovascular death in high-risk patients. The cumulative incidence of myocardial infarction/stroke/cardiovascular death is shown by the treatment group for patients with a 10-year Framingham risk score ≥20% (upper panel), 10-year systematic coronary risk evaluation risk ≥5% using the extrapolated model (middle panel), and systematic coronary risk evaluation risk ≥5% using the capped model (lower panel). NNT, number needed to treat.
Table 3  Major cardiovascular events and all-cause mortality in high-risk subgroups

|                           | Rosuvastatin | Placebo | ARR  | HR (95% CI) | P-value |
|---------------------------|--------------|---------|------|-------------|---------|
| **No. events Event rate** |              |         |      |             |         |
| **Entire JUPITER cohort (n = 8901 rosuvastatin, 8901 placebo)** |              |         |      |             |         |
| Primary endpoint           | 142 7.7      | 251 13.6| 5.9  | 0.56 (0.46–0.69) | <0.0001 |
| MI/stroke/CV death         | 83 4.5       | 157 8.5 | 4.0  | 0.53 (0.40–0.69) | <0.0001 |
| Total mortality            | 198 10.0     | 247 12.3| 2.5  | 0.80 (0.67–0.97) | 0.02    |
| **Baseline Framingham >20% (n = 786 rosuvastatin, 772 placebo)** |              |         |      |             |         |
| Primary endpoint           | 29 17.2      | 38 24.1 | 6.9  | 0.70 (0.43–1.14) | 0.155   |
| MI/stroke/CV death         | 16 9.4       | 29 18.2 | 8.8  | 0.50 (0.27–0.93) | 0.028   |
| Total mortality            | 31 17.2      | 40 23.6 | 6.3  | 0.73 (0.46–1.17) | 0.193   |
| **Baseline SCORE ≥5% (extrapolated model; n = 4619 rosuvastatin, 4683 placebo)** |              |         |      |             |         |
| Primary endpoint           | 111 11.5     | 183 18.8| 7.3  | 0.61 (0.48–0.78) | <0.0001 |
| MI/stroke/CV death         | 67 6.9       | 118 12.0| 5.1  | 0.57 (0.43–0.78) | 0.0003  |
| Total mortality            | 149 14.4     | 185 17.5| 3.2  | 0.82 (0.66–1.02) | 0.076   |
| **Baseline SCORE ≥5% (age capped at 65 years; n = 3130 rosuvastatin, 3177 placebo)** |              |         |      |             |         |
| Primary endpoint           | 71 11.1      | 130 20.1| 9.0  | 0.56 (0.42–0.74) | <0.0001 |
| MI/stroke/CV death         | 38 5.9       | 83 12.7 | 6.9  | 0.47 (0.32–0.68) | <0.0001 |
| Total mortality            | 97 15        | 135 20.6| 5.6  | 0.74 (0.57–0.96) | 0.022   |

MI, myocardial infarction; CV, cardiovascular; HR, hazard ratio; CI, confidence interval; SCORE, systematic coronary risk evaluation; ARR, absolute rate reduction. Primary endpoint, time to occurrence of first MI/stroke/cardiovascular death/arterial revascularization/unstable angina.

Data for the entire JUPITER cohort are from reference 1. Extrapolated and capped SCORE models are described in the ‘Methods’ section.

*Rates are per 1000 person-years.

Figure 2  Cumulative incidence of fatal/non-fatal myocardial infarction and stroke in high-risk patients. The cumulative incidence of fatal/non-fatal myocardial infarction and fatal/non-fatal stroke are shown by the treatment group among patients with a 10-year systematic coronary risk evaluation risk ≥5% using the extrapolated (upper panel) and capped models (lower panel).
Figure 3 Effects of rosuvastatin on myocardial infarction/stroke/cardiovascular death in high-risk patients, according to baseline characteristics. The hazard ratios and 95% confidence intervals for rosuvastatin when compared with placebo are shown for patients with Framingham risk score $\geq 20\%$ and systematic coronary risk evaluation risk $\geq 5\%$ (extrapolated and capped models). Size of the point estimate rectangle is proportional to the number of clinical events. The dashed vertical line indicates the relative risk reduction for the entire trial cohort. Also shown are $P$-values for the test of an interaction between the composite endpoint and categories within each subgroup.
Adverse events and laboratory abnormalities were consistent with the known safety profile of rosuvastatin.12

Strengths of this analysis include the randomized, placebo-controlled design, broad geographic representation including a substantial number of Europeans, and inclusion of large numbers of women and ethnic minority participants. A limitation is the post hoc selection of the higher risk subgroups, which was undertaken in response to health authority requests.4 For example, analysis of JUPITER subgroups by SCORE strata was not pre-specified in the JUPITER protocol. Global risk prediction scores can be used to direct use of preventive therapies such as statins towards patients most likely to benefit.15,16 As expected, clinical event rates in the JUPITER placebo group were higher in the high-risk Framingham or SCORE groups compared with the entire cohort for the primary study endpoint as well as for the composite of MI/stroke/cardiovascular death and all-cause mortality. The magnitude of the absolute rate reduction for clinical events was correspondingly greater in the high-risk groups (Table 3).

Two factors contributing to the observed absolute reduction in clinical events in JUPITER were the underlying event rate in the placebo group, enhanced in this case by selecting patients with high global cardiovascular risk and elevated hs C-reactive protein, and the relative risk reduction due to treatment, enhanced by use of a high-efficacy statin. The reductions in LDL-C (49%) and clinical events (43–53% for MI/stroke/cardiovascular death) with rosuvastatin in the JUPITER patients with SCORE risk ≥5% are greater than reported for other statins.17,18 Although these data support the use of high-efficacy statin therapy, they do not rather than the pre-specified JUPITER primary endpoint. Nonetheless, the relative reduction in MI/stroke/cardiovascular death with rosuvastatin was remarkably consistent across a range of baseline participant characteristics and consistent with primary trial analyses of the full study population as pre-specified in the JUPITER protocol. Global risk prediction scores can be used to direct use of preventive therapies such as statins towards patients most likely to benefit.15,16 As expected, clinical event rates in the JUPITER placebo group were higher in the high-risk Framingham or SCORE groups compared with the entire cohort for the primary study endpoint as well as for the composite of MI/stroke/cardiovascular death and all-cause mortality. The magnitude of the absolute rate reduction for clinical events was correspondingly greater in the high-risk groups (Table 3).

Two factors contributing to the observed absolute reduction in clinical events in JUPITER were the underlying event rate in the placebo group, enhanced in this case by selecting patients with high global cardiovascular risk and elevated hs C-reactive protein, and the relative risk reduction due to treatment, enhanced by use of a high-efficacy statin. The reductions in LDL-C (49%) and clinical events (43–53% for MI/stroke/cardiovascular death) with rosuvastatin in the JUPITER patients with SCORE risk ≥5% are greater than reported for other statins.17,18 Although these data support the use of high-efficacy statin therapy, they do not

Table 4  Adverse events and laboratory abnormalities in high-risk subgroups

|                      | Framingham risk >20% | SCORE risk >5% |
|----------------------|-----------------------|----------------|
|                      | RSV Placebo | Extrapolated model | Capped model |
|                      | n          | RSV Placebo | n       | RSV Placebo | n       | RSV Placebo |
| Any adverse event    | 786 (79.6) | 617 (79.9) | 3681 (79.7) | 3704 (79.1) | 2490 (79.6) | 2510 (79.0) |
| Any serious adverse  | 154 (19.6) | 153 (19.8) | 855 (18.5) | 878 (18.7) | 544 (17.4) | 587 (18.5) |
| Muscle symptoms      |            |              |            |              |            |              |
| Myalgia              | 46 (5.9)   | 41 (5.3)    | 363 (7.9)  | 303 (6.5)    | 233 (7.4)  | 183 (5.8)   |
| Myositis             | 0          | 1 (0.1)     | 3 (0.1)    | 3 (0.1)      | 3 (0.1)    | 2 (0.1)     |
| Myopathy             | 0          | 0           | 0          | 1 (0)        | 0          | 1 (0)       |
| Rhabdomyolysis       | 0          | 0           | 1 (0)      | 0            | 1 (0)      | 0           |
| Newly diagnosed cancer| 35 (4.5) | 39 (5.1)    | 195 (4.2)  | 212 (4.5)    | 116 (3.7)  | 145 (4.6)   |
| Death from cancer    | 9 (1.1)    | 11 (1.4)    | 29 (0.6)   | 48 (1.0)     | 19 (0.6)   | 40 (1.3)    |
| Gastrointestinal disorder | 206 (26.2) | 214 (27.7) | 1184 (25.6) | 1175 (25.1) | 763 (24.4) | 737 (23.2) |
| Renal disorder       | 100 (12.7) | 87 (11.3)   | 487 (10.5) | 522 (11.2)   | 355 (11.3) | 354 (11.1) |
| Hepatic disorder     | 19 (2.4)   | 14 (1.8)    | 103 (2.2)  | 101 (2.2)    | 65 (2.1)   | 57 (1.8)    |
| Investigator-reported diabetes | 24 (3.1) | 34 (4.4) | 131 (2.8) | 116 (2.5) | 84 (2.7) | 83 (2.6) |
| Laboratory values    |            |              |            |              |            |              |
| Creatinine >100% increase from baseline | 1 (0.1) | 0 | 7 (0.2) | 3 (0.1) | 6 (0.2) | 2 (0.1) |
| eGFR at 12 months (mL/min/1.73 m²) | 65.0 (14.2) | 64.4 (13.9) | 66.9 (14.2) | 66.4 (13.6) | 69.2 (14.3) | 68.7 (13.3) |
| ALT >3x ULN on consecutive visits | 3 (0.4) | 2 (0.3) | 14 (0.3) | 6 (0.1) | 12 (0.4) | 5 (0.2) |
| HbA1c at 24 months (%) | 60.0 (0.3) | 59.2 (0.53) | 59.6 (0.49) | 58.6 (0.46) | 59.7 (0.48) | 58.7 (0.46) |
| Fasting glucose at 24 months (mmol/L) | 5.7 (0.9) | 5.7 (1.3) | 5.6 (1.1) | 5.6 (0.9) | 5.6 (1.0) | 5.6 (0.9) |

Values are n (%) or mean (standard deviation). SCORE, systematic coronary risk evaluation; RSV, Rosuvastatin; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; HbA1c, glycosylated haemoglobin; ULN, upper limit of normal.
minimize the roles of diet, exercise, and smoking cessation as the most important interventions for primary prevention. Despite the benefit derived from treatment with rosuvastatin in these high-risk patients, caution should be exercised when considering treatment of patients lacking any cardiovascular risk factors. Further, long-term compliance with statin therapy is critical for efficacy among those patients where pharmacologic therapy is indicated in addition to lifestyle interventions.

Although the analyses presented here parallel those requested by European Health Authorities, they do not address most patients actually studied in the JUPITER trial. For example, among the 7340 men and women with elevated hs C-reactive protein and the Framingham risk scores of 11–20%, where the 4.5-year absolute risk of a primary endpoint was 10.6% in the placebo group, rosuvastatin was associated with a 49% reduction in risk (HR: 0.51, 95% CI: 0.39–0.68, P < 0.0001). Similarly, among the 6091 participants with entry Framingham scores of 5–10%, where the 4.5-year absolute risk was 5.3%, a 45% reduction was observed with rosuvastatin treatment (HR: 0.55, 95% CI: 0.36–0.84, P = 0.005), and among trial participants with elevated hs C-reactive protein with SCORE risk <5%, rosuvastatin was associated with a 56% reduction in vascular risk (HR: 0.44, 95% CI: 0.29–0.68). Thus, the JUPITER trial data also indicate that many individuals with elevated hs C-reactive protein who fall outside ‘high-risk’ subgroups defined by either Framingham or SCORE have both substantive absolute risk and large relative risk reductions when treated with rosuvastatin.

### Supplementary material

Supplementary material is available at European Heart Journal online.

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### Conflict of interest

During the period of this project, W.K. reports receiving research support grants from Dade–Behring and Glaxo SmithKline; lecture fees from AstraZeneca, Pfizer, Novartis, and Boehringer-Ingelheim; and consulting fees from GlaxoSmithKline and Roche. P.M.R. 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 from AstraZeneca, Novartis, Merck, Merck-Schering Plough, sanofi-aventis, ISIS, Seimens, 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 that have been licensed to Seimens and AstraZeneca.

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