

Low-risk older patients (50 years and older) with raised high-sensitivity CRP (hs-CRP) benefit from rosuvastatin therapy: the JUPITER study

Primary prevention with statins given a boost by rosuvastatin study

The JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, which tested the role of underlying low-grade inflammation using the determination of high-sensitivity C-reactive protein levels (hs-CRP) as the differential of additional risk in an otherwise healthy population, has shown that statin therapy using rosuvastatin significantly reduced the incidence of major cardiovascular events.

This study is important, as half of all myocardial infarctions and strokes occur among apparently healthy men and women with levels of low-density lipoprotein cholesterol (LDL-C) below currently recommended thresholds for

treatment (3.4 mmol/l).

The JUPITER results will undoubtedly provoke considerable discussion as to how clinicians (and funders) should incorporate these substantial and significant findings into their daily clinical practice. Certainly, clinicians cannot ignore the fact that rosuvastatin therapy in these patients with LDL-C levels lower than 3.4 mmol/l experienced fewer non-fatal myocardial infarctions (MI), non-fatal stroke, hospitalisation for unstable angina, revascularisation, and confirmed death from cardiovascular causes (Table 1, Fig. 1). In evaluating the implications of this study, it is instructive to review the salient points of the published trial, now available online,¹ and to view the supplementary index.

The trial selected 17 802 apparently healthy men and women with LDL-C levels of less than 3.4 mmol/l. These were from 89 890 screened patients, of whom 52% were ineligible because their LDL-C levels were above 3.4 mmol/l, and 36% whose hs-CRP was

below 2.0 mg/l.

Included in the study were men (50 years or older) and women (60 years or older) without a history of cardio-vascular disease. Patients were statin naïve and were excluded if they had taken lipid-lowering therapy previously or were currently on lipid-lowering therapy. Forty per cent of recruited patients had the metabolic syndrome, as defined by the American Heart Association and the NHLB Institute. The median BMI was 28 kg/m². South Africa was a major contributor of patients to the JUPITER trial and was in fact the third largest recruiter of patients (Table 2). As the study's primary objective was to include a significant number of women, black and Hispanic patients, it would be informative to know how many black patients South Africa contributed to the total of 1 100 black subjects in the study (12.4% of the study population) (Table 2). These data on the patients recruited in South Africa have not been provided.

TABLE 1. JUPITER: OUTCOMES ACCORDING TO STUDY GROUP

End point	Patients with event, rosuvastatin (n=8901), n	Patients with event, placebo (n=8901), n	Hazard ratio (95% CI)
Primary end point*	142	251	0.56 (0.46-0.69)
*Nonfatal MI	22	62	0.35 (0.22-0.58)
*Any MI	31	68	0.46 (0.30-0.70)
*Nonfatal stroke	30	58	0.52 (0.33-0.80)
*Any stroke	33	64	0.52 (0.34-0.79)
*Revascularization	71	131	0.54 (0.41-0.72)
*Hospitalization for unstable angina	16	27	0.59 (0.32-1.10)
*Revascularization or hospitalization for unstable angina	76	143	0.53 (0.40-0.70)
*MI, stroke, or death from CV causes	83	157	0.53 (0.40-0.69)
*Death on any known date	190	235	0.81 (0.67-0.98)
*Any death	198	247	0.80 (0.67-0.97)

*Primary end point: composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization, and confirmed death from cardiovascular causes


Ridker PM et al. *New Engl J Med* 2008; available at: <http://www.nejm.org>. 

TABLE 2. PATIENT NUMBERS PER COUNTRY, PARTICIPATING IN JUPITER

Country	No. of patients
United States	4 021
United Kingdom	2 873
South Africa	2 497
Canada	2 020

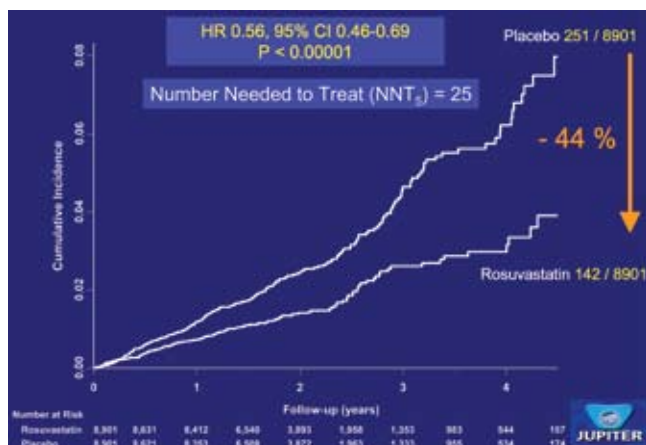



Fig. 1. Primary trial endpoint: MI, stroke, unstable angina/revascularisation, cardiovascular death.

TABLE 3. BASELINE CLINICAL CHARACTERISTICS

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
Age, years (IQR)	66.0 (60.0-71.0)	66.0 (60.0-71.0)
Female, N (%)	3,426 (38.5)	3,375 (37.9)
Ethnicity, N (%)		
Caucasian	6,358 (71.4)	6,325 (71.1)
Black	1,100 (12.4)	1,124 (12.6)
Hispanic	1,121 (12.6)	1,140 (12.8)
Blood pressure, mm (IQR)		
Systolic	134 (124-145)	134 (124-145)
Diastolic	80 (75-87)	80 (75-87)
Smoker, N (%)	1,400 (15.7)	1,420 (16.0)
Family History, N (%)	997 (11.2)	1,048 (11.8)
Metabolic Syndrome, N (%)	3,652 (41.0)	3,723 (41.8)
Aspirin Use, N (%)	1,481 (16.6)	1,477 (16.6)

All values are median (interquartile range) or N (%)



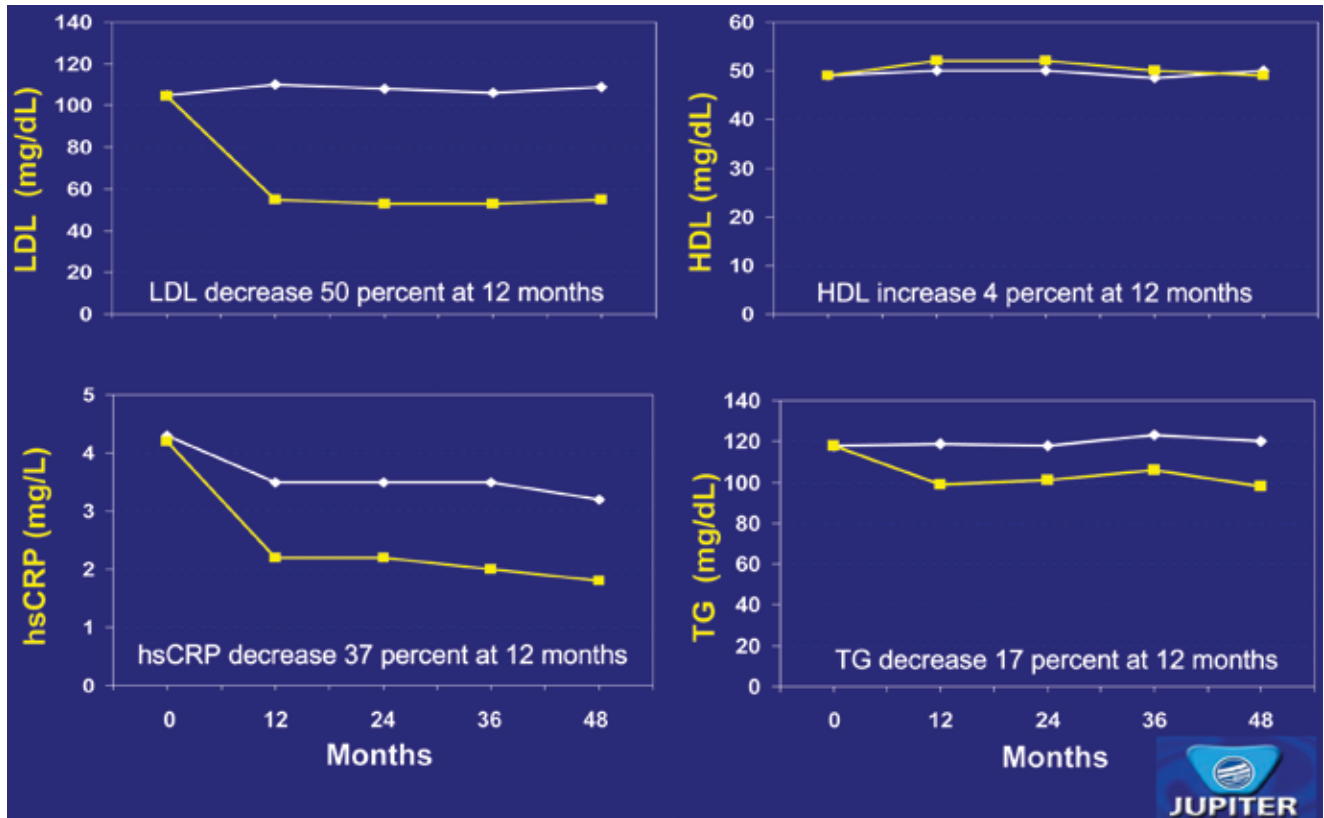


Fig. 2. Effects of rosuvastatin 20 mg on LDL-C, HDL-C, TGs and hs-CRP.

Diabetic patients, those on hormone-replacement therapy and patients with raised triglycerides were excluded from the study.

The primary outcome of JUPITER was the occurrence of the first major cardiovascular event, defined as non-fatal MI, non-fatal stroke, hospitalisation for unstable angina, and arterial revascularisation procedure or confirmed death from cardiovascular causes. The study was stopped early (30 March 2008), and all primary analyses were performed on an intention-to-treat basis. The median

follow up was 1.9 years and the maximal follow up was 5 years.

Effects of rosuvastatin on lipids and hs-CRP

At the time the study was terminated, 75% of participants were taking their study medication. The median LDL-C level at 12 months was 1.4 mmol/l (50% lower than in the placebo group) among those assigned rosuvastatin and the median hs-CRP was 2.2mg/l (37% lower than in the placebo group). Triglyceride levels were

17% lower at the 12-month visit in the rosuvastatin group, while high-density lipoprotein cholesterol (HDL-C) was 4% higher (Fig. 2).

Dr Paul Ridker of the Brigham and Women’s Hospital, Harvard, who headed the study, and discussant Dr Andrew Tonkin, National Heart Foundation, Melbourne, Australia, concurred that JUPITER has added to the robust data on statin safety. ‘Statins as a class are very effective and safe and there was no evidence of increased cancer, myopathy, renal disorders or haemorrhagic stroke

TABLE 4. ADVERSE EVENTS AND MEASURED SAFETY PARAMETERS.

Event	Rosuvastatin	Placebo	P
Any SAE	1,352 (15.2)	1,337 (15.5)	0.60
Muscle weakness	1,421 (16.0)	1,375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0.0)	--
Incident Cancer	298 (3.4)	314 (3.5)	0.51
Cancer Deaths	35 (0.4)	58 (0.7)	0.02
Hemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (ml/min/1.73m ² at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
ALT > 3xULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 mth)	98 (91-107)	98 (90-106)	0.12
HbA1c (% at 24 mth)	5.9 (5.7-6.1)	5.8 (5.6-6.1)	0.01
Glucosuria (12 mth)	36 (0.5)	32 (0.4)	0.64
Incident Diabetes**	270 (3.0)	216 (2.4)	0.01

*Occurred after trial completion, trauma induced. All values are median (interquartile range) or N (%).
**Physician reported

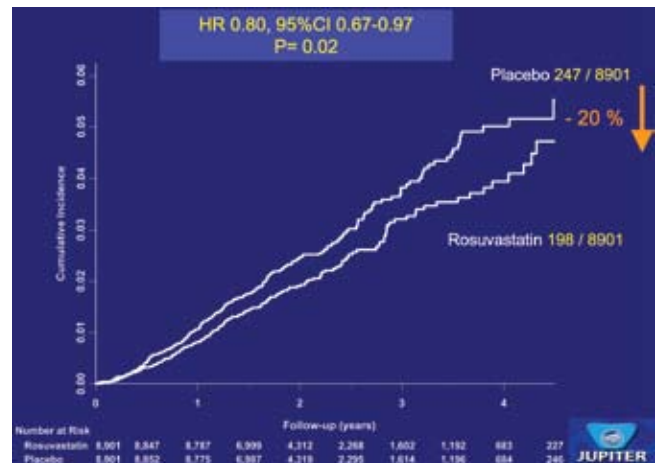


Fig. 3. Secondary endpoint: all-cause mortality.

in the patients who participated for the maximum period of five years', Dr Ridker pointed out.

Adverse events are summarised in Table 4. Physician-reported diabetes was more frequent in the rosuvastatin group but these events were not adjudicated by the end-point committee.

Benefits were observed across all subgroups, even those at Framingham risk scores of 10% or less. Importantly, the trial showed robust reductions in cardiovascular events in women, black and Hispanic populations – groups for which data on primary prevention is still limited.

The secondary endpoint of all-cause mortality (Fig. 3) was lowered by 20% in those patients receiving rosuvastatin.

1. Ridker PM, Danielson E, Fonseca FAH, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med* 2008; **359**(21): 2195–2207.

A South African expert comments on the JUPITER study

Dr Dirk Blom, specialist physician, University of Cape Town

The much-anticipated results of the JUPITER study were recently released at the American Heart Association meeting in New Orleans. The JUPITER study had been stopped prematurely after a median duration of 1.9 years, as event rates were significantly lower in patients receiving rosuvastatin 20 mg/d than those on placebo.

JUPITER was a primary-prevention statin study, in which elevated levels of hs-CRP were used for the first time as a selection criterion. Patients were eligible if they had no history of cardiovascular disease, an LDL-C of less than 3.4 mmol/l and an hs-CRP above 2.0 mg/l. Men had to be older than 50 years and the minimum age for women was 60 years. The median age of the trial cohort was 66 years. The investigators had to screen almost 90 000 patients to finally enroll 17 802.

Rosuvastatin profoundly reduced LDL-C from 2.8 mmol/l at baseline to 1.4 mmol/l at 12 months. The absolute number of major cardiovascular events (MI, cardiovascular accidents or cardiovascular death) in the rosuvastatin group was 83/8 901 (0.9%), and 157/8 901 (1.8%) in the placebo group. Rosuvastatin was well tolerated and the only safety concern was a higher rate of physician-reported new-onset diabetes (3.0 vs

2.4%) in the rosuvastatin group. This clearly requires further evaluation, as an increased incidence of diabetes would reduce the benefit of treatment.

The results of the JUPITER study are not entirely unexpected. Statins have reduced cardiovascular risk in almost all clinical settings. The magnitude of the risk reduction was larger than that predicted from meta-regression analyses of previous statin trials. However, there are statistical concerns about the validity of meta-regression analysis, and trials that terminate early are prone to overestimating benefits.

JUPITER selected patients with elevated CRP, but it was not a trial of a CRP-based risk-assessment strategy. Patients with a CRP above 2.0 mg/l benefited from treatment, but whether some patients with lower CRP levels and other markers of risk would have benefited remains unclear. CRP measurement therefore does not replace conventional risk algorithms, but may influence treatment decisions in patients with intermediate risk. For instance, patients with high cardiovascular risk (who were excluded from JUPITER) but low CRP should not be denied statins.

JUPITER adds important information to the already very extensive database on the efficacy and safety of statins. The real challenge currently is defin-

ing an optimal strategy of statin deployment. This is particularly challenging in the setting of primary prevention where potentially large numbers of patients need to be treated for many years, with significant cost implications. Primary prevention is dogged by the problem of risk assessment; we are just not very good at identifying who will have an event, and therefore needs treatment. JUPITER unfortunately does not solve the problem, but expands the pool of patients who may benefit from statins.

JUPITER shows that starting treatment relatively late in life (median age 66 years) and lowering LDL-C profoundly is effective in patients with LDL-C < 3.4 mmol/l and CRP > 2.0 mg/l. There is no reason to suspect that patients with higher LDL-C would not benefit similarly. What we don't know is whether lesser LDL-C reductions would have a similar, if slightly smaller benefit, at reduced costs. We also do not know whether larger benefits would be obtained by reducing LDL-C moderately in younger patients for longer periods of time.

What we need is a careful review of guidelines, following cost-effectiveness analyses of the JUPITER and other data, to formulate statin strategies that maximise event reduction in relationship to resource allocation.