

RAPID APPRAISAL

Name of Trial: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein

Reference: Ridker PM et al. New England Journal of Medicine 2008; 359: 2195-207

Question: Does rosuvastatin decrease the rate of first major cardiovascular events in apparently healthy people without hyperlipidaemia but with elevated high-sensitivity C-reactive protein levels?

Summary: The results of this large study (n = 17,802) demonstrated that use of rosuvastatin 20 mg/day for a median of 1.9 years reduced the absolute risk of experiencing a first major cardiovascular (CV) event in healthy subjects, as described above, by 1.2% compared with placebo (hazard ratio (HR) in favour of rosuvastatin of 0.56 (95% confidence interval (CI) 0.46 to 0.69; p < 0.00001). Reduced risk of death from any cause (HR 0.80 (95% CI 0.67 to 0.97); p = 0.02; absolute risk reduction = 0.6%), was also demonstrated. Adverse event rates were similar in the two groups, with the exception of physician-reported newly diagnosed diabetes (3.0% and 2.4% with rosuvastatin and placebo, respectively, p = 0.01, absolute risk increase = 0.6%).

A disadvantage of this study was that because of its early termination it is not certain whether the observed benefits of rosuvastatin are maintained, or the adverse effect profile would have changed, in the longer term.

Rosuvastatin is not currently licensed for primary or secondary prevention of CV disease and use in the apparently healthy population, including the associated screening, would be expensive. Robust analysis of cost-effectiveness is needed before such a prescribing policy is adopted.

Did the study ask a clearly focussed question?

Yes – The aim of this study, **Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)**, was to determine whether rosuvastatin would reduce the rate of first major cardiovascular (CV) events, compared with placebo, in apparently healthy people who had low-density lipoprotein cholesterol (LDL-C) levels below current treatment thresholds, but had elevated high-sensitivity C-reactive protein (hs-CRP) levels. The composite primary end point was the occurrence of a first major CV event, defined as: non-fatal myocardial infarction (MI), non-fatal stroke, hospitalisation for unstable angina, an arterial revascularisation procedure, or confirmed death from cardiovascular causes. There were several secondary single and composite end points: the individual components of the primary end point; arterial revascularisation or hospitalisation for unstable angina; MI, stroke, or death from CV causes; and death from any cause.¹

Was the study design appropriate?

Yes – This study was a randomised, double-blind, placebo-controlled controlled, multicentre (1315 sites in 26 countries) trial. The eligibility criteria were: men aged ≥50 years and women aged ≥60 years with no history of CV disease, LDL-C level of <3.4 mmol/L, hs-CRP level ≥2.0 mg/L and triglyceride level <5.6 mmol/L.¹

There were numerous exclusion criteria, e.g. previous or current use of lipid-lowering therapy, current use of hormone replacement therapy, evidence of hepatic dysfunction (alanine aminotransferase > twice the upper limit of normal (ULN)), creatine kinase > three times ULN, creatinine level > 176.8 micromoles/L, diabetes, uncontrolled hypertension, cancer (other than basal-cell or squamous-cell carcinoma of the skin) within five years of enrolment, uncontrolled hypothyroidism, recent history of medical conditions that might compromise safety or successful completion of the study, inflammatory conditions, immunosuppressant drugs or long-term oral glucocorticoids. Only subjects who successfully completed a four-week run-in phase, during which they took placebo, who demonstrated compliance of >80% with placebo were enrolled.¹

This trial was sponsored by the manufacturer of rosuvastatin, AstraZeneca, which also holds a licence for patents that relate to the use of hs CRP in the evaluation of patients' risk of CV disease; the lead author is listed as a co-inventor on these patents.¹

Were participants appropriately allocated to intervention and control groups?

Yes – The subjects were randomly assigned (1:1) to rosuvastatin 20 mg/day or matching placebo (n = 8901 per group). An interactive voice-response system was used for randomisation, and participants were stratified by

centre. The baseline characteristics of the two groups did not differ.¹

Were participants, staff and study personnel ‘blind’ to participants study group?

Yes – JUPITER was a double-blind trial, and all reported primary end points were adjudicated by an independent committee that was unaware of the randomised treatment assignments.¹

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes – Outcomes for all the randomised patients are reported. All primary analyses were performed on an intention-to-treat basis,¹ and all the randomised patients (including the 44 and 37 lost to follow-up in the rosuvastatin and placebo groups, respectively) were included in the efficacy and safety analyses.²

Were the participants in all groups followed up and data collected in the same way?

Yes – Follow-up visits were scheduled at 13 weeks, six months and then every six months, after randomisation up to 60 months, with a closeout visit after termination of the study. Personnel at each site also contacted their participants mid-way between these scheduled visits to evaluate their wellbeing and maintain participation.¹

Was the study large enough?

Yes – This was an event-driven trial that was designed to continue until 520 confirmed primary end points had been documented, to provide a statistical power of 90% to detect a 25% reduction in the primary end point rate, with a two-sided significance level of 0.05. Two interim efficacy analyses were pre-specified, and the stopping boundary was crossed at the first evaluation (when 393 patients had reached the primary end point). The independent data and safety monitoring board took the size (a 44% reduction in hazard compared with the predicted 25%) and precision of the observed treatment benefit, and effects on the death and other secondary end point rates into account and terminated the study early (after a median of 1.9 years, rather than the scheduled five years). Adverse event reporting was continued (blinded) for each participant until he or she attended a formal closeout visit when therapy was discontinued.¹

How are the results presented and what is the main result?

The results for each end point are presented as a hazard ratio (HR) with 95% confidence intervals (CI) for the comparison of event rates in the two groups, with p values.¹

Primary end point: In the rosuvastatin and placebo groups, 142/8901 (1.6%) and 251/8901 (2.8%) patients, respectively, experienced first major CV events. The HR for rosuvastatin was 0.56 (95% CI 0.46 to 0.69, p < 0.00001), indicating that rosuvastatin reduced the relative risk of having a

major CV event by 44%. This equates to an absolute risk reduction of 1.2%.

Secondary end points: All the reported secondary end points, except hospitalisation for unstable angina) showed significant hazard reductions (see table below). The biggest contributor to the primary end point was arterial revascularisation, which was performed in 0.8% and 1.5% of patients in the rosuvastatin and placebo groups, respectively.

Secondary end point	HR (95% CI)	p
Non-fatal MI	0.35 (0.22 – 0.58)	<0.00001
Any MI	0.46 (0.30 to 0.70)	0.0002
Non-fatal stroke	0.52 (0.33 – 0.80)	0.003
Any stroke	0.52 (0.34 to 0.79)	0.002
Arterial revascularisation	0.54 (0.41 – 0.72)	<0.0001
Hospitalisation for unstable angina	0.59 (0.32 – 1.10)	0.09
Arterial revascularisation or hospitalisation for unstable angina	0.53 (0.40 to 0.70)	<0.00001
MI, stroke or death from CV causes combined	0.53 (0.40-0.69)	<0.00001
Death from any cause	0.80 (0.67 to 0.97)	0.02

How safe was the regimen?

Serious adverse event rates were similar in the rosuvastatin and placebo groups: 15.2% and 15.5%, respectively (p = 0.60). Physician-reported diabetes occurred more frequently in the rosuvastatin (3.0%) than the placebo group (2.4%, p = 0.01), which represents an absolute risk increase of 0.6% (number needed to harm (NNH) = 167). This NNH is the same as the number needed to treat (NNT) for death due to any cause (2.2% and 2.8% in the rosuvastatin and placebo groups, respectively, absolute risk reduction = 0.6%). The median HBA_{1C} values differed very slightly, but significantly (5.9% and 5.8%, respectively, p = 0.001), but neither the fasting blood glucose level nor newly diagnosed glycosuria differed significantly during the follow-up period. Myopathic events occurred in 0.1% of the subjects in both groups (p = 0.82), and rhabdomyolysis was reported in one patient in the rosuvastatin group (a 90-year-old who had febrile influenza, pneumonia and trauma-induced myopathy). The incidences of other reported adverse effects and laboratory parameters in the two groups did not differ significantly.¹

How precise are the results?

The confidence interval for the HR for the primary end point comparison of the two groups was narrow and did not cross the line of no effect, and the p value was very low (<0.00001), which indicates good precision. The HR values for all the secondary end point results had confidence intervals that did not cross the line of no effect, and an accompanying range of p values from <0.00001 (non-fatal MI) to 0.02 (death due to any cause), with the exception of hospitalisation for unstable angina (p = 0.09).

Can the results be applied to the local population?

Probably not – The racial/ethnic mix of the study population comprised about 71% white, 12 - 13%

black, about 13% Hispanic and 3-4% other/unknown subjects.¹ Therefore, it differed from the UK population, which has a higher proportion of subjects of Asian origin and fewer Hispanic subjects. The study included 2873 UK subjects.²

In addition, only patients demonstrated to have high concordance with drug therapy were able to participate.

Does rosuvastatin decrease the rate of first major cardiovascular events in apparently healthy people with low-density lipoprotein cholesterol levels below current treatment levels but with elevated high-sensitivity C-reactive protein levels?

Rosuvastatin 20 mg/day for a median of 1.9 years reduced the absolute risk of experiencing a first major CV event by 1.2% in this population. The adverse event rates with rosuvastatin and placebo were similar, except for a 0.6% higher frequency of physician-reported newly diagnosed diabetes with rosuvastatin.

A significant limitation of this trial is that it was terminated early, at a median of 1.9 years rather than the scheduled five years. Consequently, the treatment effect could have been overestimated, it is not certain whether the observed benefit of rosuvastatin would have been maintained in the longer term, and longer term safety was not assessed. The risk-benefit ratio of potentially lifelong therapy with rosuvastatin 20 mg/day in apparently healthy subjects is therefore unknown. The possible association of rosuvastatin with the development of diabetes, in particular, requires further detailed investigation.

The dose used in the study is at the high end of the dose range. Current UK recommendations are that rosuvastatin should be started at 5 - 10 mg/day (5 mg in the elderly and patients of Asian origin, there were few or none of the latter in this trial) and increased at intervals of at least four weeks, according to clinical need.³ In England in the 12 months from July 2007 to June 2008, the most commonly prescribed strength of rosuvastatin was 10 mg (69% of all prescriptions); 20 mg accounted for only 20% of all prescriptions.⁴

A major issue raised by this trial is whether treating the defined population with rosuvastatin 20 mg/day would be cost-effective. The authors' calculated (based on Kaplan - Meier estimates) NNTs with rosuvastatin for two to five years to prevent one primary event occurring. These estimated NNT values and the costs (at current UK prices)⁵ of treating these numbers of patients with rosuvastatin 20 mg/day are shown in the table below.

Estimated NNT	Years	Cost to treat (£)
95	2	£64,446
31	4	£42,060
25	5	£42,399

In addition to drug costs, the cost of screening to identify suitable subjects needs to be taken into account (two or more hs-CRP tests may be needed, see below). The study population comprised 17,802 people, which represents only a fifth of those screened (n = 89,890); 52% were ineligible due to LDL-C levels ≥ 3.4 mmol/L and 36% had hs-CRP levels < 2.0 mg/L.¹ Current American guidelines recommend performing two hs-CRP assays two weeks apart, and averaging the results, in metabolically stable subjects without obvious infection or inflammation to reduce within-individual variability. Any result > 10 mg/L should be discarded and the test repeated two weeks later.⁶

Reduction in hospital admissions (e.g. for unstable angina or revascularisation) would offset at least some of the cost of treatment and screening. Detailed cost-effectiveness and risk-benefit analyses are required to determine whether rosuvastatin treatment would be an appropriate primary preventive strategy.

Current NICE lipid modification guidance recommends that the management of other modifiable risk factors for CV disease should be optimised, if possible, before offering lipid modification therapy for primary prevention in subjects with a 10-year CV disease risk of $\geq 20\%$.⁷ The use of hs-CRP as a CV disease risk assessment tool is not included in current NICE guidance. Current American guidance (based on expert consensus opinion) endorses the optional use of hs-CRP as an additional tool to identify patients without known CV disease who may be at higher absolute risk than estimated by major risk factors, to assist clinicians in making decisions about therapy or further evaluation.⁶

In the UK, rosuvastatin is not licensed for primary or secondary prevention of CV events.⁸ AstraZeneca plans to apply for a licence extension for rosuvastatin in 2009.⁹

Current practice for primary prevention of CV disease should not change as a result of this study, the results of which should not be extrapolated to other statins. Rosuvastatin and other statins should not be prescribed for primary prevention of CV disease in healthy low-risk individuals without hyperlipidaemia.

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