# New Australian indication for cardiovascular disease prevention with statin therapy

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*The new JUPITER-based TGA indication in Australia for rosuvastatin therapy is for the prevention of major cardiovascular events in men aged 50 years and older and women aged 60 years and older with no clinically-evident cardiovascular disease but who have at least two conventional risk factors.*

The JUPITER trial (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) investigated the benefits of high-dose statin therapy in people whose LDL cholesterol level would not meet criteria for statin therapy but whose high-sensitivity C-reactive protein (hsCRP) level was raised.[1]

The rationale for JUPITER was based on epidemiological data linking the inflammatory biomarker hsCRP to cardiovascular disease (CVD) risk and on a retrospective subgroup analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a primary prevention trial with lovastatin that showed that patients with high levels of hsCRP responded better to statin therapy than those with lower levels.[1] The response in the AFCAPS/TexCAPS trial was also greater in those patients achieving lower levels of hsCRP, independently of achieved LDL cholesterol levels.[1]

JUPITER enrolled 17,802 men and women without diabetes who had no previous CVD, hsCRP levels of 0.2 mg/L or greater, LDL cholesterol levels below 3.4 mmol/L and total triglyceride levels below 5.6 mmol/L. Subjects were randomised to treatment with rosuvastatin 20 mg daily or placebo, with an intended duration of four years.[2]

JUPITER was stopped after an average follow up of 1.9 years because of an approximate 50% reduction in major CV events in patients receiving rosuvastatin compared with placebo. Similar outcomes were observed for all subgroups.[2]

Although JUPITER was designed to include subjects at low CVD risk (other than for hsCRP levels), 59% of participants were either



## Key points

- **The results of the JUPITER trial have led to approval in Australia of a new indication for rosuvastatin therapy, broadening the range of people for whom statin therapy is indicated.**
- **The new TGA indication approves rosuvastatin therapy for the prevention of major cardiovascular disease (CVD) events in men aged 50 years and older and women aged 60 years and older with no clinically-evident CVD who have at least two conventional risk factors.**
- **The new indication broadens current PBS criteria and provides a greater opportunity for the primary prevention of CVD.**
- **The new indication does not include measurement of high-sensitivity C-reactive protein.**

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**Table. Current (May 2011) eligibility criteria for PBS subsidy of lipid-lowering drugs**

| Patient category | Lipid levels for PBS subsidy |
|---|---|
| Symptomatic<br>• coronary heart disease<br>• cerebrovascular disease<br>• peripheral vascular disease | Any cholesterol level |
| Diabetes mellitus<br>• microalbuminuria (albuminuria >20 μg/min or albumin to creatinine ratio >2.5 (males), >3.5 (females)<br>• Aboriginal and Torres Straits Islanders<br>• age 60 years or over | Any cholesterol level |
| Diabetes mellitus not included above | Total cholesterol >5.5 mmol/L |
| Family history of symptomatic CHD:<br>• at age <55 years in two or more first-degree relatives<br>• at age <45 years in one or more first-degree relatives | Any cholesterol level |
| Family history of symptomatic CHD:<br>• at age <60 years in one or more first-degree relatives<br>• at age <50 years in one or more second-degree relatives<br>and<br>Patients with familial hypercholesterolaemia and:<br>• DNA mutation, or<br>• tendon xanthomas in patient or first- or second-degree relative | If age >18 years at treatment initiation:<br>• LDL cholesterol >5 mmol/L, or<br>• total cholesterol >6.5 mmol/L, or<br>• total cholesterol >5.5 mmol/L and HDL cholesterol <1 mmol/L<br>or<br>If age <18 years at treatment initiation:<br>• LDL cholesterol >4 mmol/L |
| HDL cholesterol <1 mmol/L | Total cholesterol >6.5 mmol/L |
| Aboriginal and Torres Straits Islanders or hypertension | Total cholesterol >6.5 mmol/L, or<br>total cholesterol >5.5 mmol/L and HDL cholesterol <1 mmol/L |
| Not eligible above:<br>• men aged 35 to 75 years<br>• postmenopausal women aged 75 years or younger | Total cholesterol >7.5 mmol/L, or<br>triglycerides >4 mmol/L |
| Not otherwise included | Total cholesterol >9 mmol/L, or<br>triglycerides >8 mmol/L |

intermediate or high CVD risk by Framingham risk score, largely because of a mean age of 66 years.[2]

## Why JUPITER is important

The JUPITER trial is important for several reasons, as listed below.

- JUPITER provides the first large-scale clinical outcomes trial for rosuvastatin.
- JUPITER examined statin therapy for CVD primary prevention in patients with low LDL cholesterol but high hsCRP, patients who would previously not be considered for drug therapy.
- 20 mg rosuvastatin therapy was well tolerated. Although the duration of mean follow up was less than two years, no increased incidence of side effects was observed in subjects treated for up to five years.[2]
- The rate of myalgia was not significantly different between rosuvastatin-treated (16.1%) and placebo-treated groups (15.5%).[2] Rhabdomyolysis was reported in one rosuvastatin-treated patient (a 90-year-old subject with pneumonia and trauma-induced myopathy).[2]
- Low levels of LDL cholesterol appeared to be safe (50% of subjects had LDL cholesterol levels below 1.4 mmol/L and 25% had levels below 1.1 mmol/L).[2]
- No increase in the rate of cerebral haemorrhage occurred in the rosuvastatin-treated group (n=6) compared with the placebo-treated group (n=9).[2] This had been observed in

a previous high-dose statin study, suggesting low LDL cholesterol levels may increase risk.[3]
- Cost-benefit analyses have indicated that treatment of patients in the JUPITER trial with rosuvastatin is cost-effective.[4]
- JUPITER focused on primary prevention, which has tended to be overshadowed by the current emphasis on secondary prevention, with its more favourable cost–benefit ratio. Many more CV events can be prevented with primary prevention however, often in people at the prime of their working lives and who still have many years of productivity ahead of them. Long-term results (in terms of decades, not years) need to be considered for primary prevention strategies.
- JUPITER results have led to approval in Australia for a new indication for rosuvastatin therapy, broadening the range of people for whom statin therapy is indicated and providing a greater opportunity for primary prevention of CVD.

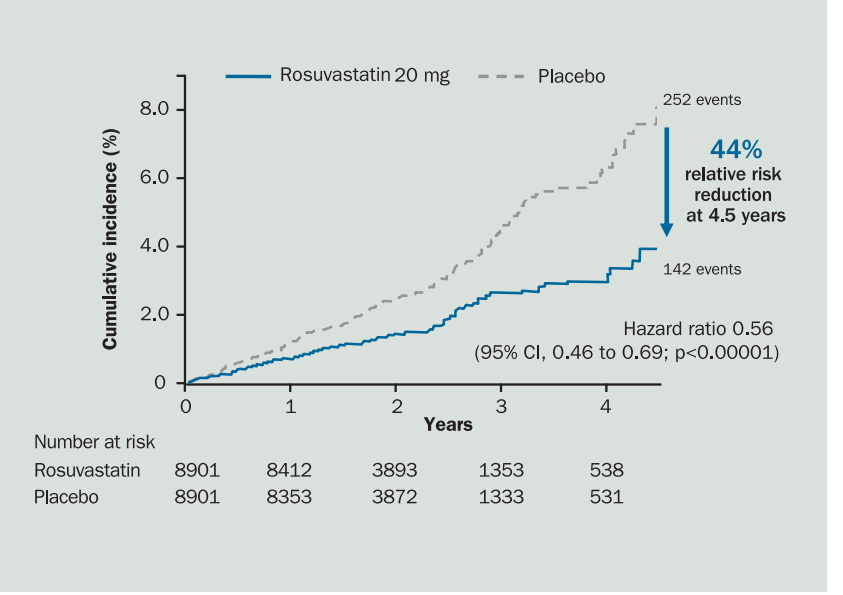


**Figure 1. Cumulative incidence of the primary end point in JUPITER.**

## The new JUPITER-based indication

In April 2011, the TGA in Australia approved a new indication for rosuvastatin as below.

- Rosuvastatin is indicated for the prevention of major CVD events in men aged 50 years and older or women aged 60 years and older with no clinically evident CVD but with at least two conventional risk factors for CVD (hypertension, low HDL cholesterol, smoking or a family history of premature CHD). It is indicated to reduce the risk of nonfatal myocardial infarction, reduce the risk of nonfatal stroke and reduce the risk of coronary artery revascularisation.

Under the new indication, patients with hypertension who are aged 50 years or more (men) and 60 years or more (women) and who have low HDL cholesterol or a family history of premature coronary heart disease or who are smokers are suitable for rosuvastatin therapy, irrespective of lipid levels. Furthermore, patients with low HDL cholesterol who are aged 50 years or more (men) and 60 years or more (women) and who have hypertension or a family history of premature coronary heart disease or are smokers are suitable for rosuvastatin therapy, irrespective of lipid levels. No initial trial of diet or lifestyle modification is required.

Current (May 2011) PBS eligibility criteria for lipid therapy do not include measurements of absolute risk but allow patients at very high CVD risk to be eligible at any cholesterol level (Table). The new indication broadens the indications for lipid therapy but until PBS subsidy is approved for the new indication, rosuvastatin must be prescribed privately for appropriate patients.

The new indication for rosuvastatin therapy does not include patients with diabetes mellitus, metabolic syndrome or obesity, all of whom had similar primary endpoint relative risk reductions in JUPITER.[2] About 40% of JUPITER patients met US criteria for metabolic syndrome.[1]

As in Europe, the new Australian indication for rosuvastatin does not include measurement of hsCRP, unlike the recent US indication for the drug.[5,6] Exclusion of hsCRP measurement may be because:

- hsCRP is not often measured for risk assessment in Australia
- hsCRP assay and reporting are not standardised in different laboratories
- hsCRP interpretation is not well understood
- there is debate as to the validity of hsCRP as a CVD risk marker
- hsCRP levels vary considerably within an individual with time
- hsCRP is a nonspecific acute phase reactant that is increased by inflammation of any kind.

Furthermore, hsCRP has not been a consistent marker of CVD risk in all studies. In the Heart Protection Study of patients with CHD or type 2 diabetes, baseline hsCRP did not predict response to simvastatin.[7] This may reflect a difference in the role of hsCRP in the two populations of patients, and does not exclude the possibility of a distinct property of rosuvastatin different from other statins.[8]

JUPITER was not a scientific trial of hsCRP; this would have required inclusion of another group with normal or low levels of hsCRP. At the time of planning JUPITER, post hoc data from the AFCAPS/TexCAPS trial showed no benefit with statin therapy in patients with low levels of LDL cholesterol and low levels of hsCRP, so this group was not included in JUPITER.[1]

## JUPITER and the 2005 Australian Position Statement on Lipid Management

According to the 2005 National Heart Foundation of Australia/ Cardiac Society of Australia and New Zealand (NHFA/ CSANZ) Position Statement on Lipid Management, lipid-modifying drug therapy is indicated for those individuals estimated to be at a 15% or greater absolute risk of a CVD event in the next five years.[9]

Drug therapy should be considered in those estimated to be at 10 to 15% risk of a CVD event in the next five years in the presence of either of the following:

- family history of premature CHD (first-degree relative who developed CHD before age 60 years)
- metabolic syndrome.

Current PBS eligibility criteria are consistent with neither the NHFA/CSANZ guidelines nor the new indication for rosuvastatin therapy, and private prescriptions are required under both recommendations to access statin therapy.

## CVD endpoints in JUPITER

The cumulative incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, arterial revascularisation, hospitalisation for unstable angina or confirmed death from cardiovascular causes) in JUPITER is shown in the Figure.[2] Treatment with rosuvastatin 20 mg resulted in a 44% relative risk reduction with a five-year number needed to treat (NNT) of 25.[2]

Prespecified subgroup analysis showed the benefit to be consistent for all groups, including gender, age (65 years and younger, or over 65 years), smoking status, ethnicity, the presence of hypertension, those with or without a family history of CHD, those with normal weight, overweight or obesity, the presence of metabolic syndrome and Framingham risk score (10% and below, or above 10%).[2]

## JUPITER adverse effects

Adverse effects occurred in the JUPITER trial with similar rates for placebo and statin groups. There was a lower rate of cancer deaths in the rosuvastatin group. Although statistically significant, numbers were too small to draw a meaningful conclusion. There was a slight increase in the rate of newly-diagnosed diabetes in the rosuvastatin group, consistent with previous statin trials.[10] The absolute risk of diabetes was low, however, especially when compared with the reduction in coronary events.[2]

In view of the increased incidence of type 2 diabetes, routine monitoring of weight, waist circumference, blood glucose level and $HbA_{1c}$ levels is recommended in men aged 50 years or more and women aged 60 years or more treated with statins. Patients with metabolic syndrome should be assessed more frequently and efforts made to improve insulin sensitivity by weight control and dietary modification, with use of metformin for the obese if required.

## Cost-effectiveness of JUPITER

Treatment of JUPITER patients with Framingham risk score 10% or above has been reported as being cost effective.[4] However, treatment with statins over a 10-year period was not cost effective for people with 10-year CVD risk below 5%.[4]

## Summary

The new TGA indication for the use of rosuvastatin broadens the availability of lipid therapy compared with current PBS eligibility criteria, although at the moment rosuvastatin must be prescribed privately for appropriate patients. Previous statin trials (most of which used LDL cholesterol level criteria for enrolment) reported reduction in vascular risk of about 20% for each 1 mmol/L absolute reduction in LDL cholesterol level after 12 months of treatment.[11] A similar relation was observed in JUPITER, which adds to the evidence base supporting the use of statins for primary prevention of CVD in people who would not previously have TGA approval for drug therapy. The 2005 NHFA/CSANZ Position Statement on Lipid Management recommends drug therapy for patients with intermediate Framingham risk and coexistent metabolic syndrome or family history of premature CVD. Many of the patients enrolled in JUPITER met these criteria and consideration of statin therapy would seem appropriate for such patients. CT

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COMPETING INTERESTS: Professor Hamilton-Craig is a member of the Cardiac Society of Australia and New Zealand Council on Genetic Cardiovascular Diseases, Australian Atherosclerosis Society Committee on Familial Hypercholesterolaemia, US National Lipid Association, Queensland Lipid Group, European Atherosclerosis Society, EMPOWER and ADVANCE Advisory Boards for prostate and breast cancer, and Lipid Advisory Boards of Merck Sharp & Dohme (Australia), Astra Zeneca (Australia), and Solvay/Abbott (Australia). He has received travel grants and honoraria from multiple sources including pharmaceutical companies.