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# Statins as primary prevention in patients without dyslipidaemia

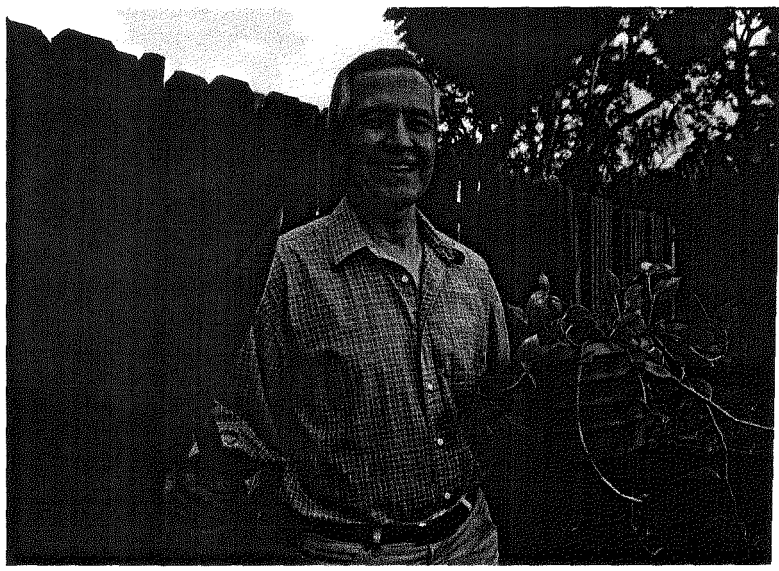
*By Leanne Stafford and Dr Luke Bereznicki,*

## Learning objectives

After reading this article you should be able to:

- Discuss the use of statins for the primary prevention of cardiovascular disease.
- Describe the emerging evidence linking the benefits of statins to factors other than cholesterol reduction alone.
- Consider the implications of recent research on statin prescribing in the Australian population.

**Competencies addressed: 3.1.2, 3.1.3, 3.2.2, 4.2.1, 4.2.2, 4.2.3.**



*Mr VW is a 62-year-old regular customer of your pharmacy. He is not overweight, runs 10km three times a week ...*

## Case study

*Mr VW is a 62-year-old regular customer of your pharmacy. He is not overweight, runs 10km three times a week, eats healthily, does not smoke and controls his hypertension with quinapril* (Accupril) *10mg daily. He was recently shocked when his 63-year-old long-time friend suffered a massive heart attack while playing golf at the local country club and died before the ambulance arrived, so he underwent a full medical check-up and was given a clean bill of health. Although his GP has assured him that his cholesterol levels are completely normal, his wife has 'read somewhere that he perhaps should have another blood test and be taking a statin medication anyway'.*

## Introduction

Cardiovascular disease (CVD) remains the leading cause of death in Australia, responsible for 34% and 39% of male and female deaths, respectively.[1] It is also a significant contributor to the burden of disease across the population. Dyslipidaemia, especially elevated levels of low-density lipoprotein cholesterol (LDL-C), is recognised as a major cardiovascular risk factor. Statins have become firmly established as first-line lipid lowering therapy in the secondary prevention of established CVD due to their ability to lower LDL-C levels and improve patient outcomes.[2] Numerous large randomised controlled trials have also demonstrated the benefits of statins in the primary prevention of CVD.

## Statins in primary prevention

A recently published meta-analysis of 19 randomised clinical trials, representing the most comprehensive meta-analysis of statin therapy for primary prevention to date, aimed to confirm the benefits of statins in patients with no previous history of CVD.[3] For inclusion in this analysis, the trials had to have been of a minimum of 12 months' duration, enrolled a majority of patients with no history of CHD and not include high-risk diabetic patients, who already possess an excessively elevated risk of cardiovascular morbidity and mortality. Almost 64,000 patients were included in the meta-analysis, which demonstrated a 7% relative risk reduction in all-cause mortality (RR 0.93, 95% CI: 0.87 to 0.99, p=0.03) with statin use. Significant reductions were also noted in the risk of cardiovascular death, fatal and all myocardial infarction (MI), major cardiovascular events, stroke and the requirement for revascularisation (angioplasty or coronary

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artery bypass grafting). The conclusions of this study supported those of three previous meta-analyses of statin therapy in primary CVD prevention, all of which demonstrated variable reductions in major coronary events and mortality.[4-6]

## Mechanism of protective benefit: LDL vs CRP

The focus of statin therapy in recent years has shifted from consideration of total cholesterol levels to treating to target LDL-C levels. The justification for this aggressive treatment strategy has been the accumulation of evidence that there is a linear relationship between LDL-C concentrations and rates of cardiac events.[7] While observed more strongly in secondary prevention studies and in diabetics, this trend has also been noted in primary prevention studies.

The previously described meta-analysis, however, failed to demonstrate an association between a reduction in LDL-C and morbidity or mortality, leading the authors to question whether the major benefit of statins is actually not due to LDL reduction.[3] This is not a unique perspective. Many investigators have described statins as possessing a variety of 'pleiotropic' properties that are thought to convey protective benefits unrelated to changes in lipid levels. These properties include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, modulation of inflammatory responses, stabilisation of atherosclerotic plaques and prevention of thrombus formation.[8]

Investigation of the pleiotropic effects of statins has also focussed on their effects on high-sensitivity C-reactive protein (hs-CRP). Coronary heart disease is increasingly being viewed as an inflammatory process.[7] CRP, as an acute phase reactant,[9] is elevated in the setting of inflammation. More importantly, it is believed to be directly involved in both the early initiation of atherosclerotic lesions and in the conversion of stable to unstable plaques.[10] The proposed roles of CRP in the atherosclerotic process include augmentation of the inflammatory response; activation of the expression of adhesion molecules and the potent chemokine, monocyte chemoattractant protein-1; attenuation of expression of endothelial nitric oxide synthase; plasminogen activator inhibitor-1 induction and direct effects on arterial thrombosis.[10]

Clinically, hsCRP levels have been shown to be independently associated with various other uncontrolled cardiovascular risk factors including glucose, triglyceride and HDL-C concentrations, blood pressure and body mass index.[11]

## hsCRP in clinical trials

The relationship between hsCRP levels, statins and the progression of CHD has been further explored in both secondary and primary prevention studies.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, which investigated the early initiation of high dose atorvastatin therapy (80mg daily) in patients with non-ST elevation acute coronary syndromes (ACS), patients' hsCRP levels were found to be significantly raised upon entry into the study and significantly reduced after 16 weeks' treatment with atorvastatin (compared to placebo).[12] Baseline hsCRP levels were highest in patients with below-median baseline LDL-C levels and hsCRP was reduced to approximately the same extent in all patients irrespective of baseline LDL-C. These findings supported a potent antiinflammatory effect of high-dose atorvastatin in patients suffering from ACS, independent of LDL cholesterol levels.

AFCAPS/TexCAPS was a primary prevention trial of lovastatin (a statin not marketed in Australia) conducted in patients with average total cholesterol levels and below-average cardioprotective high density lipoprotein cholesterol (HDL-C) levels.[10] This trial not only demonstrated a 37% relative risk reduction in fatal or nonfatal MI, hospitalisation for unstable angina or sudden cardiac death in this population with lovastatin administration, but also produced a number of interesting observations regarding hsCRP levels in the setting of primary prevention. These included the following:

- coronary event rates increased with baseline hsCRP levels;
- statin administration resulted in a statistically significant reduction in hsCRP levels after one year of treatment, a reduction unrelated to the effect on lipid levels; and
- lovastatin was effective in reducing coronary events not only among patients with high LDL-C levels, but also those with low LDL-C but elevated hsCRP levels.[10]

These findings, indicating that statins may be effective in the presence of systemic inflammation even in the absence of dyslipidemia, have been corroborated in a number of other clinical settings. They have led some physicians to advocate for widespread hsCRP screening as part of cardiovascular risk assessment, and the initiation of statin therapy for primary prevention of cardiovascular events in patients with elevated hsCRP levels, even if their LDL levels are within target ranges.[10]

## JUPITER

It is against this background that JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a randomised, double-blind, placebo-controlled, multicentre trial, was conceived.[13] JUPITER was designed to evaluate whether treatment with rosuvastatin 20mg daily, compared with placebo, would decrease the rate of first major cardiovascular events in patients with no previous history of cardiovascular disease, 'normal' LDL-C levels (less than 3.4 mmol/L) but elevated hsCRP levels (2.0 mg/L or higher).

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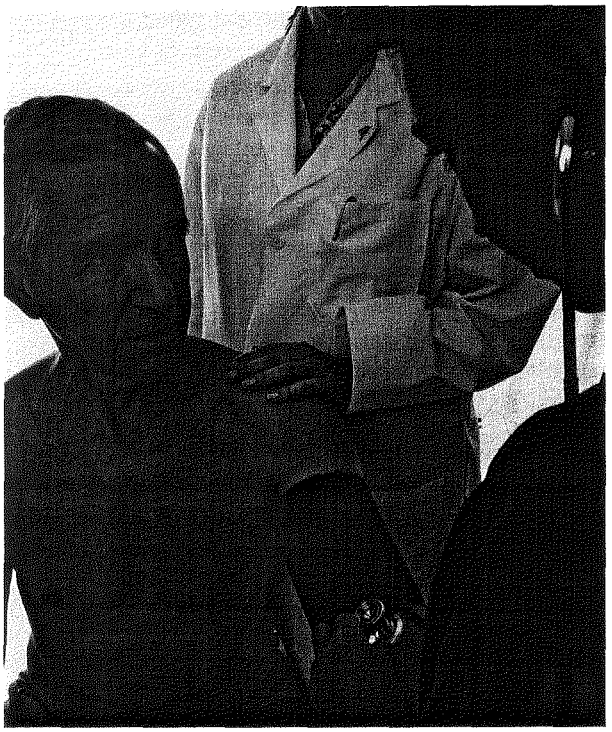
The trial was stopped prematurely after a median follow-up of 1.9 years on the recommendations of an independent data monitoring board and the JUPITER steering committee. This early termination was based on 'unequivocal evidence of a reduction in cardiovascular morbidity and mortality' in patients in the rosuvastatin arm.[13] Among these patients, rosuvastatin produced 50% and 37% reductions in LDL-C and hsCRP levels, respectively. Treatment was associated with a 44% reduction in the composite risk of cardiovascular death, stroke, MI, hospitalisation for unstable angina or revascularisation rates compared to placebo. Extrapolation of these results suggests that 25 patients would need to be treated with rosuvastatin for five years to prevent one of these events. Even patients at very low risk (non-smokers, not overweight, no metabolic syndrome, or Framingham cardiovascular risk score of 10% or less) benefitted from rosuvastatin therapy.

## Implications ... and the future

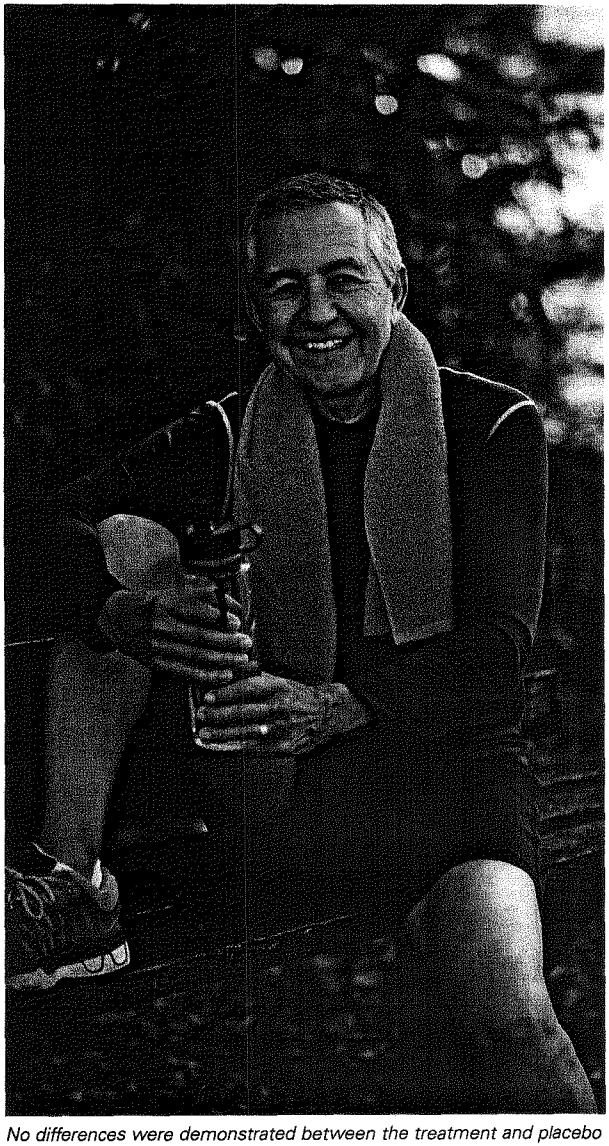
Almost half of all cardiovascular events occur among apparently healthy patients with normal or even low levels of LDL-C.[10] JUPITER thus has the potential to significantly alter clinical practice guidelines for the primary prevention of cardiovascular disease. Translation of the study's findings into clinical practice, however, would also have significant financial ramifications for healthcare systems across the developed world. A recent analysis estimated that an additional 19.2% of the adult American population, or 11 million patients, would meet the JUPITER criteria for statin therapy.[14] Another group of researchers, using the 1999-2002 National Health and Nutrition Examination Survey (NHANES) data, calculated that 7.4 million adult Americans (4.3% of the adult American population) met the JUPITER entry criteria, and to treat this entire cohort with rosuvastatin would cost $US8.9 billion per year.[15] Statins already represent a major cost to the Australian Pharmaceutical Benefits Scheme (PBS), with atorvastatin, simvastatin and rosuvastatin first, second and eighth on the list of top 10 drugs by cost subsidised by the Australian Government in 2007-08.[16] The PBS qualifying criteria currently severely restrict statin prescribing in the 'low risk' population of patients without symptomatic cardiovascular disease, diabetes or other significant cardiovascular risk factors to those with grossly elevated total cholesterol or triglyceride levels.[17] Extending statin prescribing into this population by applying the JUPITER criteria would therefore have the potential to greatly increase statin-related costs to the PBS.

An editorial accompanying the JUPITER study also cautioned on the indiscriminate acceptance of JUPITER's results, attempting to place them in clinical perspective.[18] Although treatment with rosuvastatin was associated with a very large relative risk reduction, the absolute risk reduction was only 1.2%, or 0.9% for the 'hard' cardiovascular outcomes of cardiovascular death, MI and stroke.[18,19] JUPITER was not designed to evaluate the effect of hsCRP measurement on patients' outcomes, nor did it compare the use of hsCRP with other markers of cardiovascular risk. Potential benefits in patients with hsCRP levels less than 2mg/L were also not investigated. Furthermore, only 17,802 of the 89,890 people (19.8%) screened for enrolment in the study actually reached randomisation, which has implications for wide-scale hsCRP screening.[18] hsCRP may also be elevated in other forms of inflammation, from rheumatoid arthritis to inflammatory bowel disease to infection, so alternative diagnoses must be considered in the interpretation of the result.[9]

Consideration must be given to potential safety concerns regarding rosuvastatin prescribing in this asymptomatic patient population. The dose of rosuvastatin used in the study was 20mg daily, the maximum recommended dose in Australia without specialist supervision.[20] The early termination of JUPITER precluded evaluation of the long-term safety of this dosage regimen and degree of LDL-C reduction. No differences were demonstrated between the treatment and placebo groups in the rates of myopathy or cancer, which was in contrast to one previously published study demonstrating an inverse relationship between cancer incidence and achieved LDL-C levels.[21] There was, however, an increase in glycosylated haemoglobin levels and the incidence of physician-reported diabetes observed in the rosuvastatin group during JUPITER which require further investigation.[13]



*Even patients at very low risk (non-smokers, not overweight, no metabolic syndrome, or Framingham cardiovascular risk score of 10% or less) benefitted from rosuvastatin therapy.*



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Another unanswered question relates to whether hsCRP reduction and the associated clinical benefits can be considered a class effect of statins or are related to the intensity of the statin regimen. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, patients received either a moderate statin regimen (pravastatin 40mg daily) or intensive therapy (atorvastatin 80mg daily). The intensive regimen was demonstrated to reduce the risk of death, MI, unstable angina with hospitalisation, revascularisation after 30 days, or stroke by 16%, but this was not attributed to the difference in acute reductions in LDL-C levels, which was not as significant as that demonstrated in other trials.[22] Atorvastatin, however, reduced hsCRP levels significantly more than pravastatin within the first month of therapy, suggesting that regimen intensity may be important in determining the degree of hsCRP reduction and the subsequent clinical outcome.[11]

The current US guideline for hsCRP measurement is that it may be measured in asymptomatic individuals at intermediate risk based on standard clinical risk markers, if the result may influence the prescribing decision.[23] The recommendations from the National Heart Foundation of Australia (which, admittedly, have not been revised since 2005) are that the need for lipid-lowering therapy be based on calculation of cardiovascular risk, and that while hsCRP levels are independently related to the risk of future CHD events, 'there is insufficient data to indicate the benefit of targeting hsCRP with treatment, it is premature to use CRP routinely in the assessment of CVD risk, or to propose a particular goal for treatment'.[24]

For now, it appears that the implications of the results of the JUPITER trial, impressive though they may be, are too uncertain and potentially expensive for them to be incorporated into mainstream clinical practice. Patients such as Mr VW do not qualify for rosuvastatin as a Restricted Benefit on the PBS and would thus face the cost of a

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monthly private prescription. Until the results of JUPITER are confirmed by further clinical trials, ongoing attention to healthy lifestyle choices and regular reassessment of overall cardiovascular risk may be the best options for such patients. The decision to proceed with hsCRP testing as part of this risk assessment, and subsequently with statin therapy if indicated according to the JUPITER criteria, is currently one to be left to individual patients and prescribers after careful consideration of the patient's own unique risk-benefit equation.

## References


1. Vos T, Begg S. The burden of cardiovascular disease in Australia for the year 2003. National Heart Foundation of Australia; Jul 2007.
2. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease 2007. Guidelines for preventing cardiovascular events in people with coronary heart disease: National Heart Foundation of Australia; updated 2008.
3. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments. A network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol 2008;52(22):1769-81.
4. HMG Co A reductase inhibitors (statins) in the primary prevention of cardiovascular disease. Vancouver: British Columbia: Canadian Agency for Drugs and Technologies in Health; 2007.
5. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:2307-13.
6. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess 2007;11(14):1-160, iii-iv.
7. Opie LH, Commerford PJ, Gersh BJ. Controversies in stable coronary artery disease. Lancet 2006;367:69-78.
8. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004;109(suppl III):III-39-III-43.
9. Warrell DA, Cox TM, Firth JD, Benz Jr EJ, editors. Oxford textbook of medicine. 4th ed ed. Oxford: Oxford University Press; 2003.
10. Ridker PM, on behalf of the JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Rationale and design of the JUPITER trial. Circulation 2003 2003;108:2292-7.
11. Ray KK, Cannon CP, Cairns R, Morrow DA, Rifai N, Kirtane AJ, et al. Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005;46:1417-24.
12. Ray KK, Cannon CP, Ganz P. Beyond lipid lowering: What have we learned about the benefits of statins from the acute coronary syndromes trials? Am J Cardiol 2006;98(suppl):18P-25P.
13. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195-207.
14. Spatz ES, Canavan ME, Desai MM. From here to JUPITER. Identifying new patients for statin therapy using data from the 1999-2004 National Health and Nutrition Examination Survey. Circ Cardiovasc Qual Outcomes 2009;2:41-8.
15. O'Riordan M. One in five middle-aged adults newly eligible for statins based on JUPITER. Medscape Medical News [serial on the Internet] 2009 [cited February 16, 2009]. Available from: www.medscape.com/viewarticle/586800.
16. Anon. Top 10 drugs. Aust Prescr 2008 2008;31:164.
17. Australian Government Department of Health and Ageing. General statement for lipid-lowering drugs prescribed as Pharmaceutical Benefits; 2009 [cited 2009 February 15]; Available from: www.pbs.gov.au/html/healthpro/browseby/explanatory-notes?ref=section2-gec10.
18. Hlatky MA. Expanding the orbit of primary prevention - Moving beyond JUPITER. New Engl J Med 2008;359(21):2280-2.
19. O'Riordan M. AHA 2008: JUPITER hits New Orleans: Landmark study shows statins benefit healthy individuals with high CRP levels. Medscape Medical News [serial on the Internet] 2008 [cited February 15, 2009]. Available from: www.medscape.com/viewarticle/583269.
20. AstraZeneca Pty Ltd. MIMS Full Prescribing Information: Crestor. 2 September 2008.
21. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. Insights from large randomized statin trials. J Am Coll Cardiol 2007;50(5):409-18.
22. Wiviott SD, de Lemos JA, Cannon CP, Blazing M, Murphy SA, McCabe CH, et al. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. Circulation 2006;113:1406-14.
23. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.
24. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Position Statement on Lipid Management-2005. Heart Lung Circ 2005;14:275-91.