

Managing residual risk in patients receiving statin therapy

Brett D Montgomery

TO THE EDITOR: Evidence is beginning to accumulate on the effectiveness of the low-density lipoprotein (LDL) cholesterol-lowering medicine ezetimibe. While there are no completed trials investigating ezetimibe's effect on clinically important end points, two recent trials investigating its effect on carotid intima media thickness (CIMT) have both reported disappointing results.^{1,2} After each of these trials, the Journal has published editorials by Hamilton-Craig, who offers reassurance about ezetimibe and encourages ongoing prescription of this drug to patients who have elevated LDL levels despite maximum-tolerated statin therapy.^{3,4} Such a sanguine opinion seems at odds with the negative trial evidence, and therefore worthy of debate.

Briefly, the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, which compared ezetimibe plus simvastatin with simvastatin treatment alone in 720 patients with familial hypercholesterolaemia, found no significant difference (and a trend in the direction of harm) with respect to the primary end point of CIMT.¹ The ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 — HDL and LDL Treatment Strategies in Atherosclerosis) trial compared ezetimibe with extended-release niacin in statin-treated patients with coronary heart disease.² Among 315 patients with available results, the group taking niacin showed a statistically significant reduction in CIMT, but the group taking ezetimibe showed no such reduction. Of concern, increased cumulative exposure to ezetimibe was associated with progression of CIMT ($P=0.05$). Although far from definitive, the results of these two trials offer no reassurance of benefit from ezetimibe and, in my view, may portend harm.

It may seem counterintuitive that ezetimibe, which significantly lowers LDL cholesterol levels,^{1,2} could be ineffective or harmful. However, the history of medicine is replete with examples of interventions that improve numerical disease measures without benefit to patients. One recent example was torcetrapib, which, despite

increasing high-density lipoprotein cholesterol and reducing LDL cholesterol levels in a promising manner, was found to cause serious adverse events, including death.⁵

I agree with Hamilton-Craig that we require trials measuring major cardiovascular events to really understand the effects of ezetimibe. Where we disagree is how to manage our patients during the period of uncertainty until publication of the results of these trials. While he argues for continued prescribing of ezetimibe, I suggest we should explicitly share our uncertainty about the safety and efficacy of this drug with our patients by discussing the existing research. Some patients will, like Hamilton-Craig, place their faith in the cholesterol hypothesis and be reassured by an assumption of cardiovascular protection as their LDL falls. Others will choose to wait until we have more robust evidence that ezetimibe is safe and effective. I would wait.

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1 Kastelein JJ, Akdim F, Stroes ES, et al; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358: 1431-1443.

2 Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 — HDL and LDL Treatment Strategies in Atherosclerosis). Final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol* 2010; 55: 2721-2726.

3 Hamilton-Craig IR. After ENHANCE: the cholesterol hypothesis is alive and well [editorial]. *Med J Aust* 2008; 189: 303-304.

4 Hamilton-Craig IR. Managing residual risk in patients receiving statin therapy [editorial]. *Med J Aust* 2010; 192: 366-367.

5 Barter PJ, Caulfield M, Eriksson M, et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; 357: 2109-2122. □

Ian R Hamilton-Craig

IN REPLY: I agree with Montgomery that cardiovascular disease (CVD) outcomes are required to determine the role of ezetimibe. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (in which patients with aortic stenosis were treated for 52.2 months with statin plus ezetimibe or statin plus placebo) showed a 4.7% reduction in ischaemic CVD events in the ezetimibe group ($P=0.02$; number needed to treat, 23), driven by a reduced need for

coronary artery bypass grafting.¹ In contrast to previous trials showing regression of atherosclerosis in response to statin therapy, baseline carotid intima media thickness (CIMT) levels in the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial were normal, due to previous statin therapy. This is likely to account for the lack of change in CIMT with ezetimibe treatment in the ENHANCE trial.² As no placebo group was included, neither lack of benefit nor harm from ezetimibe therapy can be inferred.²

Data from animal studies have shown atherosclerosis regression after ezetimibe treatment through multiple mechanisms.³⁻⁵ Prospective randomised controlled trials with statins, resins or surgery have independently shown an approximate 1% reduction in CVD per 1% reduction in low-density lipoprotein cholesterol (LDL-C) level. Evidence for the benefits of lowering LDL-C is among the most robust in medicine. Pending the outcomes of IMPROVE-IT (the Improved Reduction of Outcomes: Vytorin Efficacy International Trial, a multicentre study of ezetimibe plus simvastatin versus simvastatin treatment of patients with acute coronary syndrome [<http://clinicaltrials.gov/ct2/show/NCT00202878>]), or clinical outcome data confirming those of the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 — HDL and LDL Treatment Strategies in Atherosclerosis) trial,⁶ it seems reasonable to continue to use ezetimibe to lower LDL-C levels in patients who are not achieving LDL-C targets despite statin therapy or who are intolerant to statins. Extended-release nicotinic acid (Niaspan [Abbott Laboratories, Chicago, Ill, USA]) may be an appropriate alternative to statins as second-line therapy, and should be made available under the Pharmaceutical Benefits Scheme for treating patients with dyslipidaemia. (Niaspan has approval from the Therapeutic Goods Administration for marketing in Australia, but is not being imported into Australia at this stage.)

Competing interests: Ian Hamilton-Craig has served on lipid advisory boards for Merck Sharp and Dohme, Solvay/Abbott and AstraZeneca, and has received speaker fees and reimbursement for travel/accommodation expenses to attend scientific meetings from these companies. He has also received honoraria from these companies and from Novartis, Pfizer, Schering Plough and Servier for presentations at postgraduate scientific meetings.

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- 1 Hamilton-Craig I, Kostner K, Colquhoun D, Woodhouse S. At sea with SEAS: the first clinical end-point trial for ezetimibe, treatment of patients with mild to moderate aortic stenosis, ends with mixed results and more controversy. *Heart Lung Circ* 2009; 18: 343-346.
- 2 Stein EA. Low-density lipoprotein cholesterol reduction and prevention of cardiovascular disease. *Mayo Clin Proc* 2009; 84: 307-309.
- 3 Kuhlencordt PJ, Padmapriya P, Rützel S, et al. Ezetimibe potently reduces vascular inflammation and arteriosclerosis in eNOS-deficient ApoE ko mice. *Atherosclerosis* 2009; 202: 48-57.
- 4 Gómez-Garre D, Muñoz-Pacheco P, González-Rubio ML, et al. Ezetimibe reduces plaque inflammation in a rabbit model of atherosclerosis and inhibits monocyte migration in addition to its lipid-lowering effect. *Br J Pharmacol* 2009; 156: 1218-1227.
- 5 Dietrich T, Hucko T, Bourayou R, et al. High resolution magnetic resonance imaging in atherosclerotic mice treated with ezetimibe. *Int J Cardiovasc Imaging* 2009; 25: 827-836.
- 6 Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 — HDL and LDL Treatment Strategies in Atherosclerosis). Final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol* 2010; 55: 2721-2726. □

Correction

Acknowledgements omitted: In “A multimodal intervention to improve fragility fracture management in patients presenting to emergency departments” in the 2 August 2010 issue of the Journal (*Med J Aust* 2010; 193: 149-153), the acknowledgements were omitted. The following text should be inserted before “Competing interests”:

Acknowledgements: We wish to thank the following for their contribution to our project: the National Health and Medical Research Council's National Institute of Clinical Studies and Australian Department of Veterans' Affairs Fellowship Program; the North Metropolitan Area Health Service, Perth (Sir Charles Gairdner Hospital, Osborne Park Hospital and area rehabilitation and aged care staff); and physicians and general practitioners involved in developing the consensus guidelines. □