Managing residual risk in patients receiving statin therapy

Marilyn K Mann

To the Editor: I am writing about important errors contained in a letter of reply by Hamilton-Craig.[1] In his response to a letter by Montgomery,[2] he states:

> 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 [cardiovascular disease] events in the ezetimibe group ($P = 0.02$; number needed to treat, 23), driven by a reduced need for coronary artery bypass grafting.

However, in the SEAS trial, patients were treated with statin plus ezetimibe *or* with placebo, not with *statin plus placebo*. Therefore, the reduction in ischaemic events in the statin/ezetimibe group cannot be attributed to ezetimibe, as it could have been caused by the effect of simvastatin alone (or by the combined effect of the two drugs). I note also that the absolute reduction in ischaemic events over the course of the trial was 4.4% (15.7% v 20.1%), not 4.7%.[3]

With respect to the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, Hamilton-Craig states:

> As no placebo group was included, neither lack of benefit nor harm from ezetimibe therapy can be inferred.[1]

In the ENHANCE trial, patients with familial hypercholesterolaemia were treated with simvastatin plus ezetimibe or simvastatin plus placebo. There was no significant difference in progression of mean carotid intima media thickness (CIMT) between the two groups (0.0058 mm in the simvastatin/placebo group v 0.0111 mm in the simvastatin/ezetimibe group [$P = 0.29$]).[4] Therefore, contrary to Hamilton-Craig's statement, there *was* a placebo group, and a lack of benefit from ezetimibe *was* shown in the trial.

Thus, the SEAS trial was unable to confirm a benefit of ezetimibe, as the active treatment arm included both a statin and ezetimibe, while the ENHANCE trial showed no additional benefit of ezetimibe on the surrogate endpoint of CIMT progression in patients taking a statin.

Author's note: The United States Securities and Exchange Commission disclaims responsibility for any private publication or statement of any Commission employee or Commissioner. This letter expresses my views and does not necessarily reflect those of the Commission, the Commissioners, or other members of the Commission staff.

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1 Hamilton-Craig IR. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375-376.
2 Montgomery BD. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375.
3 Rossebø AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359: 1343-1356.
4 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. ❑

Brett H Forge

To the Editor: I would like to endorse the letter by Montgomery[1] questioning the efficacy of ezetimibe. As yet there are no data to support its use in clinical trials using carotid intima media thickness (CIMT) as a measure of treatment effectiveness, and there is also some evidence to suggest it could be harmful.

A randomised trial conducted by Berneis et al[2] suggested that ezetimibe may induce an unfavourable pro-atherogenic low-density lipoprotein (LDL) subfraction profile by increasing small, dense LDLs.

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial[3] compared simvastatin/ezetimibe 40/10 mg daily with placebo, so any benefit from that treatment may have been from either the ezetimibe or the simvastatin. It tells us nothing about the effectiveness of ezetimibe alone.

Until the results of clinical trials are available, I believe ezetimibe should be used with much reluctance and only considered as a last resort. I agree with Hamilton-Craig[4] that it is a matter of concern that slow-release niacin, which is effective and safe, is not available under the Pharmaceutical Benefits Scheme in Australia. Searching for supplies of this drug in Australia or overseas seems the best option for treating patients whose levels of LDL cholesterol are inadequately controlled with statin therapy.

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1 Montgomery BD. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375.
2 Berneis K, Rizzo M, Berthold HK, et al. Ezetimibe alone or in combination with simvastatin increases small dense low-density lipoproteins in healthy men: a randomized trial. *Eur Heart J* 2010; 31: 1633-1639.
3 Rossebø AB, Pedersen TR, Allen C, et al. Design and baseline characteristics of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. *Am J Cardiol* 2007; 99: 970-973.
4 Hamilton-Craig IR. Managing residual risk in patients receiving statin therapy [letter]. *Med J Aust* 2010; 193: 375-376. ❑

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In reply: In the interests of scientific exactitude, I am indebted to Marilyn Mann for corrections regarding the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. However, as the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial did not include the control group ezetimibe versus placebo, the effects of ezetimibe on carotid intima media thickness remain somewhat speculative.[1]

Competing interests: I have served on lipid advisory boards for Merck Sharp and Dohme, Solvay/Abbott and AstraZeneca, and have received speaker fees and reimbursement for travel/accommodation expenses to attend scientific meetings from these companies. I have 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 Stein E. After ENHANCE: is more LDL cholesterol lowering even better? *Clin Chem* 2008; 54: 940-942. ❑