Beyond lipid-lowering therapy: does ezetimibe enhance the effects of statins on atherosclerosis?

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'Pending large prospective clinical outcome trials, surrogate measures for identifying atherosclerotic progression are often used to assess the risk of future cardiovascular events.'

Given the close relationship between serum cholesterol and cardiovascular risk, it is unsurprising that lipid-lowering therapy has been shown to markedly reduce cardiovascular events in various studies of diverse populations at cardiovascular risk [1–3]. There is up to a 19% reduction in cardiovascular events for every 1.0-mmol reduction in the level of low-density-lipoprotein cholesterol (LDL-C) [4]. Studies with coronary angiography and intravascular ultrasound have even shown regression in atherosclerotic plaque burden after intensive lipid-lowering strategies – for example, with statins [5].

Nonetheless, does 'the lower the better' apply in our approach to lipid lowering? This is particularly relevant given the availability of drugs, such as niacin or ezetimibe, that act synergistically with the HMG CoA inhibitors (statins) in further reducing lipid levels. For example, ezetimibe is a relatively new class of lipid-lowering agent that reduces the absorption of cholesterol by inhibiting the NPC1L1 receptors in the gut wall. There is greater reduction in LDL-C and improved high-density-lipoprotein cholesterol (HDL-C) concentrations when ezetimibe is used in combination with statins [6,7].

Pending large prospective clinical outcome trials, surrogate measures for identifying atherosclerotic progression are often used to assess the risk of future cardiovascular events. Carotid intima-media thickness (CIMT), measured using B-mode ultrasonic imaging, has been proposed as a useful marker in the assessment of disease progression [8,9]. An annual increase in CIMT of 0.33 mm predicts a threefold increased risk of future coronary events [8].

Thus, CIMT has often been used as a surrogate index in lipid-lowering studies. For example, more potent high-dose statins achieve greater improvements in CIMT measurements [10]. In the ARBITER-2 trial, mean CIMT after 1 year of therapy increased significantly in statin-treated patients who were randomized to add-on treatment with placebo, but no change was seen with 'add-on' niacin (p = 0.23), although the difference between these rates was not statistically significant (p = 0.08) [11]. Cardiovascular events occurred in 3.8% of patients receiving niacin and in 9.6% of placebo subjects (p = 0.20). More recently, torcetrapib (a new class of lipid-modulating drugs that act as inhibitors of cholesterol ester transfer protein) in combination with atorvastatin was compared with atorvastatin monotherapy in patients with heterozygous familial hypercholesterolemia (RADIANCE-1 [12]) and mixed hyperlipidemia (RADIANCE-2 [13]), but despite a significant reduction in LDL-C and increase in HDL levels in the torcetrapib-treated group, there was no reduction in the progression of atherosclerosis as measured by CIMT compared with monotherapy with statins.

Ezetimibe has also been tested in this manner, and the recent Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerotic Regression (ENHANCE) trial [14] generated considerable debate amongst the medical community, as well as great public and media interest. The primary aim of the study was to assess the progression of atherosclerosis using CIMT in patients with familial hypercholesterolemia treated with high-dose simvastatin (80 mg), who were then randomized to ezetimibe 10 mg or placebo. The combination therapy arm had a greater reduction in LDL-C levels (16.5% group difference), triglycerides (6.5% group difference) and C-reactive protein (30% group difference) compared with monotherapy with statins, but, despite this, there were no significant changes in the CIMT measurements over the 2-year follow-up period.

This raises the question of whether combination therapy is still an effective strategy in arresting the progression of atherosclerotic vascular disease and, subsequently, clinical outcomes. In addition, how effective is CIMT measurement as a surrogate marker of atherosclerosis? As discussed by Brown *et al.*, none of the CIMT intervention

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studies of 2 years' duration or shorter have demonstrated an effect on clinical end points, and much longer studies are required [15]. The possibility arises that prior statin therapy amongst ENHANCE participants may have led to lipid depletion and stabilization in (early) carotid plaque and, thus, 'extra' CIMT changes by adding ezetimibe may have been difficult to achieve. However, in the 19% of statin-naive subjects entered into ENHANCE, no difference was seen in CIMT between the ezetimibe- or placebo-treated arms [15]. The possibility also arises that the pleiotropic effects of statins contribute to CIMT regression, and drugs resulting in additional improvements in lipid profile *per se* (with no pleiotropic effects) may be less effective in atherosclerosis regression. As recently highlighted by Nicholls *et al.*, statin therapy is best associated with regression of atherosclerosis when LDL-C is substantially reduced and, in addition, HDL-C is increased by more than 7.5% [16].

`(In the ENHANCE trial) the combination therapy arm had a greater reduction in LDL-C levels , triglycerides and C-reactive protein compared with monotherapy with statins.'

In a recent population-based cohort study, there has been a significant increase in the prescription of ezetimibe in USA (0.1% in 2001 to 15.2% in 2006) and Canada (0.2 % in 2003 to 3.4% in 2006) for primary and secondary prevention – undoubtedly with increased overall costs, but with uncertain clinical and cost–effectiveness benefit [17]. In the UK, the NICE guidelines on ezetimibe use state that ezetimibe monotherapy should be reserved for patients with heterozygous familial and non-familial hypercholesterolemia who have contraindications to taking statins or are intolerant to statins, and can be used as combination therapy with statins if LDL-C concentration is not well controlled either after maximum dose titration of statins or if the dose titration is limited by intolerance [18]. This remains a reasonable approach to ezetimibe use, pending large clinical outcome trials.

Studies such as the IMProved Reduction of Outcomes: Vytorin® (ezetimibe and simvastatin) Efficacy International Trial (IMPROVE-IT), a multicenter, double-blind, randomized, controlled trial comparing combination therapy (Vytorin) versus simvastatin in high-risk patients presenting with acute coronary syndrome [101], and the Arterial Biology for the Investigations of the Treatment Effects of Reducing Cholesterol-6 (ARBITER-6) trial [19], should offer more information on cardiovascular outcomes and the effectiveness of using CIMT as a surrogate of coronary events. Time will tell.

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