Structural and functional manifestations of human atherosclerosis: do they run in parallel?

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This editorial refers to 'A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study', by T.F. Lüscher et al., on page 1590

Lüscher and colleagues have presented the much-awaited results of the ENCORE II multicentre trial. Its intent was to determine whether long-acting nifedipine, given in addition to statins, reverses endothelial dysfunction and retards progression of coronary atherosclerosis over 18–24 months in patients with stable coronary artery disease (CAD). Considered broadly, this study investigated the relationship between functional and structural expression of atherosclerosis. Coronary endothelial function was assessed with acetylcholine, a measure of nitric oxide (NO) bioavailability (see Figure 1). In 214 patients, as compared with placebo, nifedipine significantly improved coronary endothelial function. ENCORE II reinforces the conclusions of ENCORE I which found improved coronary endothelial function after just 6 months of nifedipine treatment and in the absence of background statins. The consistency of these findings indicates that multicentre trials of coronary endothelial testing yield reproducible results when conducted by capable investigators. While confirming the ENCORE I results, ENCORE II also demonstrates that the nifedipine-induced improvement in endothelial function persists for 2 years. Furthermore, as study drugs were washed out in advance of the follow-up endothelial testing, nifedipine appears to have favourably altered the biology of human atherosclerosis. In ENCORE II, change in coronary plaque volume was assessed by intravascular ultrasound (IVUS). In 193 patients, nifedipine as compared with placebo failed to retard the increase in plaque volume (1.0 vs. 1.9% increase in plaque size, nifedipine vs. placebo, respectively, \( P = \) non-significant). Thus, while nifedipine improved coronary endothelial function, it did not alter the progression of atherosclerosis. As endothelial function and atherosclerosis progression are both viewed as ‘barometers of cardiovascular risk’, the apparent dissociation between endothelial function and structural atherosclerosis in ENCORE II may not seem at first glance very satisfying. However, this result suggests that endothelial function and measures of structural atherosclerotic progression provide distinct and complementary insights into the pathogenesis of cardiovascular disease. The one caveat is whether ENCORE II, while adequately powered for the endothelial arm of the study, may have lacked power for showing a difference between treatment groups with respect to IVUS.

Relationship between endothelial function and structural atherosclerosis progression

Endothelium, in part through NO, retards atherosclerosis in experimental and clinical studies. In hypercholesterolaemic mice, loss of NO through a genetic deficiency of endothelial NO synthase markedly accentuates atherosclerotic plaque formation. Among human cardiac transplant recipients, loss of NO bioavailability, as detected by acetylcholine testing, is followed by rapid development of coronary arteriosclerosis. Endothelial function assessed by flow-mediated dilation in the brachial artery predicts progression of carotid intima-media thickness (IMT) even after adjustment for individual risk factors or the Framingham Risk Score. In sum, these studies suggest that endothelial function predicts and probably controls atherosclerotic plaque formation. Calcium channel blockers may improve endothelial function by reducing oxidative stress, increasing NO bioavailability, and augmenting endothelial progenitor cell numbers and function. ENCORE II sought to examine whether these potential improvements in coronary endothelial function translate into direct effects on atherosclerosis.

The effect of calcium channel blockers on progression of atherosclerosis assessed by angiography

Prior to ENCORE II, the effect of calcium channel blockers on the progression of coronary atherosclerosis was assessed initially by...
three large placebo-controlled angiographic trials. In the Montreal Heart Institute trial that tested nicardipine and in the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT) study that tested nifedipine, these calcium channel blockers did not influence the overall rate of atherosclerosis progression. However, in a retrospective analysis of these trials, the use of calcium channel blockers was associated with less progression of early lesions. In contrast, in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), amiodipine failed to slow the progression of early coronary atherosclerotic lesions, the primary endpoint of this study. In sum, the angiographic trials of calcium channels blockers have yielded contradictory results, probably due to the limitation of angiography in monitoring the growth of early atherosclerotic lesions indirectly through changes in luminal size. In contrast, ultrasound-based techniques can assess changes in plaque size far more directly and accurately.

The effect of calcium channel blockers on progression of atherosclerosis assessed by ultrasound

A substudy of PREVENT tested the effect of amiodipine on the progression of carotid artery IMT measured by ultrasound. Compared with placebo, amiodipine significantly slowed IMT progression over 36 months. The Comparison of Amlodipine vs.

Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study evaluated the effect of amiodipine on cardiovascular events and on the progression of coronary atherosclerosis assessed by IVUS in normotensive subjects with CAD. Compared with placebo (n = 95), only a trend toward less progression of atherosclerosis was observed with amiodipine (n = 91) (P = 0.12), with significantly less progression noted in the subjects with systolic blood pressure greater than the median of 129 mmHg (P = 0.02). Thus, calcium channel blockers show more promise in slowing atherosclerosis when assessed with ultrasound than with angiography, but a definitive, robustly powered IVUS trial was sorely needed.

The effect of long-acting nifedipine on progression of coronary atherosclerosis in ENCORE II

ENCORE II was intended to be such a definitive study, although it had several enormous challenges to overcome. As statins reduce the progression of atherosclerosis, the modern-day requirement to assess nifedipine in the background of statins significantly increased the required sample size. In fact, in the placebo group of ENCORE II, the plaque size increased by a mere 1.9% over 18–24 months, providing little ‘signal’ to work with. Initially, the study was designed to randomize patients into three arms of 200 patients each: cerivastatin 0.2 mg/day, cerivastatin 0.8 mg/day and cerivastatin 0.8 mg/day plus long-acting nifedipine 30–60 mg/day. The first patient entered the trial in June 1999. Due to the withdrawal of cerivastatin necessitated by its muscle toxicity, ENCORE II investigators were forced to modify the protocol at the study midpoint, with some subjects unwilling to continue. The trial resumed recruiting as an investigation of the effects of long-acting nifedipine compared with placebo on the background of statins administered according to current guidelines. The investigators deserve kudos for implementing this rescue plan and completing the study in January 2004. Nevertheless, they ended up with fewer patients than originally intended. The planned sample size of 200 patients per arm was reduced by half; while the number of patients studied was adequate for the endothelial endpoints, there may not have been enough patients to demonstrate a difference for the IVUS endpoint of ‘percentage change in plaque volume’. In addition, the IVUS field has evolved since ENCORE II was designed in the 1990s with respect to measured endpoints for atherosclerosis formation. Published in 2004, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study compared the effect of two different intensities of statin therapy on coronary plaque progression assessed by IVUS in 502 subjects with CAD. The primary endpoint of the study, percentage change in plaque volume (similar to the endpoint in ENCORE II), favoured the intensive therapy, but only with a P-value of 0.02. A secondary endpoint, change in the ‘percentage atheroma volume’, an indicator of the percentage of the overall arterial volume occupied by plaque, favoured the intensive therapy far more rigorously, with \( P < 0.001 \). The endpoint of percentage atheroma volume, by incorporating both the plaque size and the artery size into a single measure, accounts simultaneously for progression of
The effect of long-acting nifedipine on clinical outcomes in patients with CAD

With apparently contrasting effects of a calcium channel blocker on endothelial function and progression of atherosclerosis in ENCORE II, more insights might be gleaned from examining the clinical efficacy of this therapy in placebo-controlled clinical trials. CAMELOT randomized 1991 patients with CAD to amlodipine or placebo for 24 months. In these trials, calcium channel blockers reduced the frequency of angina and revascularization procedures. These effects are consistent with enhanced endothelial vasodilator function leading to improved myocardial perfusion. However, in these studies, calcium channel blockers failed to show a benefit on myocardial infarction or coronary mortality. The lack of an effect of nifedipine on atherosclerosis progression in ENCORE II might be consistent with the failure of this therapy to alter these rigorous clinical endpoints. Regression of atherosclerosis observed by IVUS tends to be modest in magnitude, yet it may reflect depletion of plaque lipid or a reduction in the size of necrotic core. These compositional changes are the cornerstones of plaque stabilization. Accordingly, one might postulate that the lack of an effect of nifedipine on atherosclerosis progression in ENCORE II suggests a lack of compositional changes commonly associated with plaque stabilization.

In conclusion, the authors are to be congratulated on bringing this study to a fruitful conclusion in the face of tremendous obstacles. ENCORE II extends the findings from ENCORE I by demonstrating long-term benefits of nifedipine on endothelial function, in the background of statin use. Whether or not calcium channel blockers retard atherosclerotic progression, as one might expect if functional and structural changes in atherosclerosis occurred in parallel, still requires further study.

Conflict of interest: none declared.

References