Low-Density Lipoprotein Cholesterol Lowering Therapy and Established Atherosclerosis

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It is well established that lipid-lowering therapy with statins has an effect on the primary and secondary prevention of ischemic coronary events that is mediated by a decrease in low-density lipoprotein cholesterol (LDL-C).1-3 Recent trials have further demonstrated reduced progression of atherosclerotic plaques with intensive statin therapy.4-6 These trials showed that the changes in plaque volume and LDL-C decrease are positively correlated and an aggressive lipid-modulating strategy can reverse the progress of atherosclerotic disease. Plaque stabilization achieved by modifying plaque composition with statin therapy has also been reported and the degree of change in plaque composition positively correlated with changes in LDL-C.6,7 On the basis of these findings, LDL-C levels <100 mg/dl are recommended for the secondary prevention of myocardial infarction by the American Heart Association and also by the Japanese Circulation Society.

In their study, 89 patients with stable angina were randomized in a 1:1 ratio to the aggressive group (dual hypolipidemic therapy: atorvastatin 80 mg + ezetimibe 10 mg) or standard dose of statin therapy. Because of the differences in statin doses between the 2 groups, it might be possible that focusing on LDL-C alone is insufficient. Moreover, in the JUPITER trial of patients with normal LDL-C levels, but increased levels of high-sensitivity C-reactive protein (hs-CRP), rosuvastatin significantly reduced the incidence of major cardiac events.8 In addition, a recently published pooled analysis revealed that diabetic subjects continued to demonstrate greater increases in atheroma volume, but both intensive lowering of LDL-C and intensive lowering of CRP had a favorable impact on plaque progression.9,10 Another observational study showed that improving control of glycemic, lipid, and inflammatory markers with the peroxisome proliferator-activated receptor-gamma agonist, pioglitazone, slows progression of carotid intimal medial thickness without decreasing LDL-C level.11 These findings suggest that treatment strategies guided by LDL-C level might not always be sufficient to achieve regression or stabilization of established atherosclerosis. Finally, it must be noted that Kovarnik et al compared patients treated with atorvastatin 80 mg and ezetimibe 10 mg with patients treated with standard doses of statins (atorvastatin 10 mg). Because of the differences in statin doses between the 2 groups, it might be under-powered to evaluate the precise role of ezetimibe in atherosclerosis regression and alteration of atherosclerotic plaque composition.

Notwithstanding these limitations, their report provides potentially interesting information that needs to be validated prospectively in larger cohorts of patients. Several questions remain: How to decrease? How much decrease? Which is the more justifiable approach to decreasing LDL-C in established atherosclerosis? What is the essential significance of LDL-C lowering alone in plaque regression or stabilization? Furthermore, it remains possible that focusing on LDL-C alone is insufficient. The point in question remains uncertain and warrants further investigation.

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