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Editorial

Are Patients with Low Non-HDL Cholesterol "Non-responders" to Statin Therapy on Coronary Plaque Regression?

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Relationship between coronary plaque progression, as determined by intravascular ultrasound (IVUS), and prospective risk for cardiovascular events has been proven by the analysis of six clinical trials[1]. IVUS studies showed only a minimal improvement of atheroma volume with statin therapy[2]. A meta-analysis of nine studies using virtual histology IVUS (VH-IVUS) imaging with 16 treatment arms and 830 participants (737 in statin and 93 in placebo) showed that statin therapy reduced plaque volume, external elastic membrane volume, and fibrous plaque volume; however, that did not affect lumen volume, fibro-fatty, and necrotic core[3]. The changes in plaque volume induced by statins were not associated with baseline levels of LDL cholesterol (LDL-C)[3]. Wakabayashi *et al.*[4] reported a subanalysis of the TRUTH study, a prospective, open-labeled, randomized, multicenter trial of VH-IVUS study that compared the effects of intensive lipid-lowering therapy with 4 mg/day of pitavastatin versus moderate lipid-lowering therapy with 20 mg/day of pravastatin for 8 months on coronary artery plaque composition in statin-naïve patients with stable or unstable angina pectoris. They investigated how baseline non-high-density lipoprotein cholesterol (non-HDL-C) levels affect the efficacy of statin therapy on plaque regression. Non-HDL-C reflects cholesterol contents of both LDL and other atherogenic lipoproteins such as very low density lipoprotein and remnant lipoproteins. The latter lipoprotein cholesterol is positively associated with triglycerides. The patients were divided into the following three groups based on non-HDL-C levels at baseline: low, ≤140 mg/dl, $n=38$; moderate, 141–169 mg/dl, $n=42$; and high, ≥170 mg/dl, $n=39$. The patients in the low non-HDL-C group were significantly older and had a significantly lower body mass index as compared to those in the higher non-HDL-C groups. Furthermore, slightly more patients treated with pitavastatin and slightly more patients with stable CAD were seen in the low non-HDL-C group. Although non-HDL-C and LDL-C at 8-month follow-up decreased to 87±19 and 67±18 mg/dl, respectively, in the low non-HDL-C group, percent atheroma volume and fibrous tissue significantly increased, whereas plaque regression was noted in the moderate and high cholesterol groups. After adjusting for all variables, a low non-HDL-C level at baseline (≤140 mg/dl) was an independent predictor of coronary plaque progression under statin therapy. Other substudies from the TRUTH study investigated several factors that affect plaque progression under statin treatment[5-7]. The study of 101 patients whose serum levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and dihomo-gamma-linolenic acid were measured, showed that decreases in EPA/AA and EPA+DHA/AA ratios were significantly associated with plaque progression based on plaque volume and fibrous component[5]. Another study of 33 patients who achieved an on-treatment LDL-C level of <70 mg/dl showed that LDL-C and apolipoprotein B levels were significantly lower in patients with plaque progression ($n=16$) compared with those in patients with plaque regression ($n=17$), and significant decreases in the n-3 to n-6 polyunsaturated fatty acid ratios compared with the baseline were seen only in patients with plaque progression[6]. Another substudy showed that age was a significant predictor of plaque progression, although the external elastic membrane volume and plaque volume were significantly greater in patients aged ≥65 years than those in the patients aged <65 years[7]. These confounding factors might affect the present results; however, it is sug-

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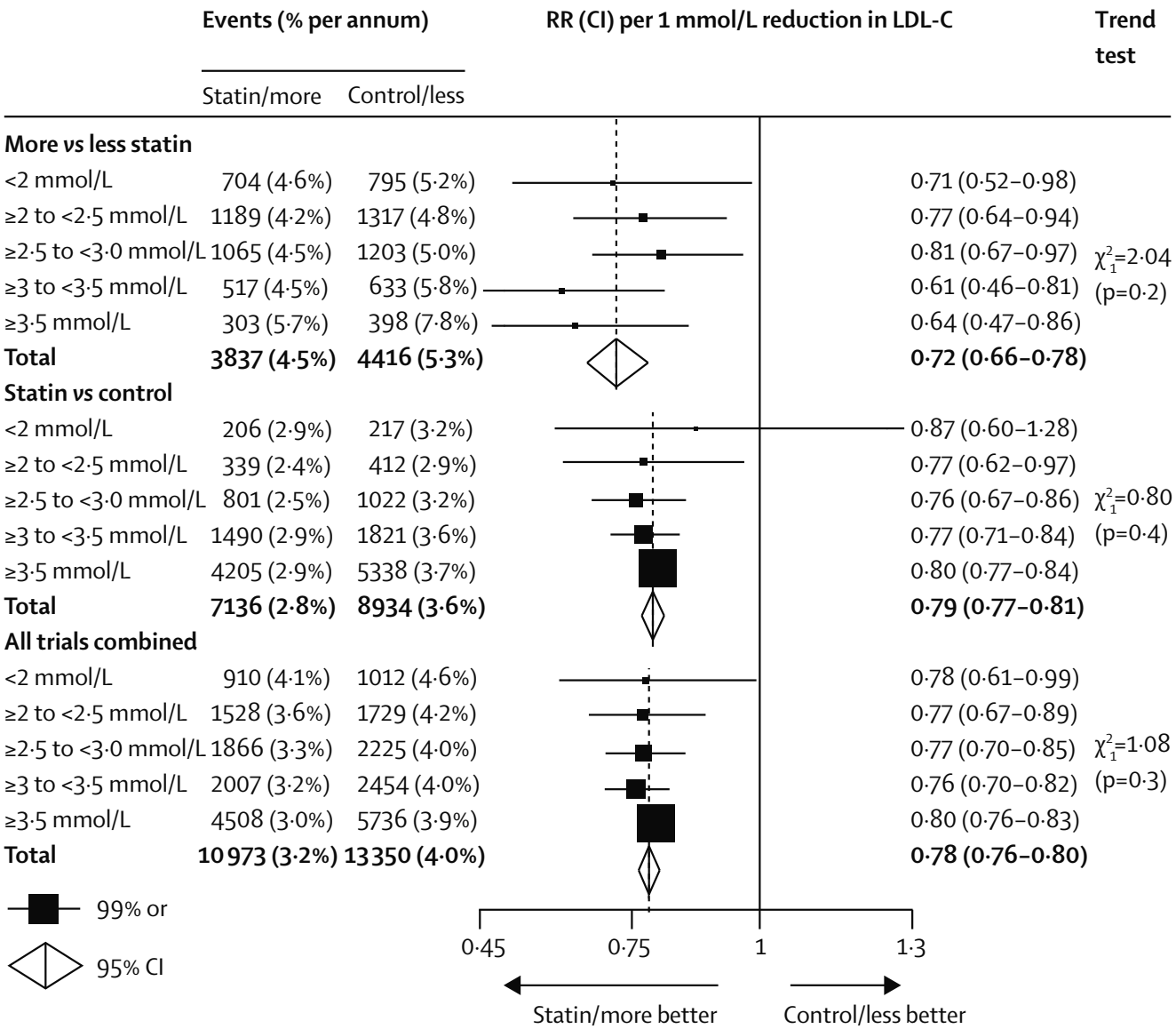

Fig. 1. Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol concentration on the less intensive or control regimen.

Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups and are weighted per 1·0 mmol/L (38.67 mg/dL) LDL cholesterol (LDL-C) difference at 1 year. Analyses were done with trial-specific and subgroup- specific LDL weights for each baseline LDL cholesterol category. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs. (Baigent C, *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376: 1670−1681[8]).

gested that we should pay attention to the cholesterol levels at baseline to consider the beneficial effects of statin therapy.

The meta-analysis of data from 170,000 participants in 26 randomized trials by the Cholesterol Treatment Trialists' Collaboration, which included 5 trials that compared more versus less intensive statin therapy, demonstrated that reductions in LDL-C reduced the incidence of major coronary events, revascularizations, and ischemic strokes and that these reductions in vascular risk can be safely achieved even in individuals with low LDL-C concentrations[8]. However, the beneficial effects might be attenuated in some patients with lower LDL-C at baseline (**Fig. 1**). It has been suggested that a low LDL-C level is associated with poor prognosis in patients with acute myocardial infarction (AMI) and heart failure. Recent reports of both a retrospective analysis of AMI patients

from Tokyo CCU Network Database[9] and a prospective, multicenter study of AMI patients[10] demonstrated that lower LDL-C level at baseline predicted short- and long-term adverse events in statin-naïve patients. It is well recognized that patients with higher baseline LDL-C levels can have a larger reduction of LDL-C level and more beneficial effects of statins, and this phenomenon is more pronounced in statin-naïve patients. Future studies are required to identify patients who have experienced less beneficial effects from statin therapy.

Disclosures

The authors have no conflicts to declare.

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