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Lipid-lowering and Anti-inflammatory Benefits of Statin Therapy: More Than Meets the Plaque

Viviany R. Taqueti, MD, MPH[*] and **Paul M Ridker, MD, MPH**[+]

Cardiovascular Imaging Program, Division of Cardiovascular Medicine[*+], Center for Cardiovascular Disease Prevention[+], Division of Nuclear Medicine and Molecular Imaging[*], Departments of Medicine and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

The benefits of statin therapy have proven so effective that patients with atherosclerosis are counseled to remain on treatment indefinitely.[1] Because the precise mechanisms by which statins exert a survival benefit are incompletely explained by their effect on serum lipids,[2] intense efforts have focused on inflammatory effects, both systemically and locally at the plaque itself.

In this issue of Circulation: Cardiovascular Imaging, Kwon and Kang et al.[3] report a post-hoc analysis of the prospective, single-center STABLE (Statin and Atheroma Vulnerability Evaluation) trial,[4] in which patients in Seoul, Korea underwent invasive coronary angiography with intravascular ultrasound (IVUS) at baseline and 12 months following 1:2 randomization to rosuvastatin 10 mg vs. 40 mg daily. Only those patients (n=312) with coronary stenoses defined by virtual histology (VH)-IVUS as fibroatheroma-containing lesions were enrolled, and 225 patients completed the protocol. The primary report of the STABLE trial concluded that patients on either dose of rosuvastatin demonstrated lesions with reduced frequencies of thin-cap fibroatheroma (TCFA), decreased percent necrotic core volume, and increased percent fibrofatty volume on follow-up evaluation.[4]

In the current analysis, investigators explored the relationship between the changes observed in VH-IVUS-defined characteristics of index plaque with two critical biomarkers, low-density lipoprotein cholesterol (LDLC) and high-sensitivity C-reactive protein (hsCRP). As would be anticipated in a statin trial, levels of LDLC and hsCRP decreased robustly (105.7 to 67.1 mg/dl and 2.2 to 1.2 mg/l, respectively) from baseline to follow-up. In analyses stratified by quartiles of change in hsCRP and LDLC, linear associations with changes in plaque characteristics (percent necrotic core and dense calcium volumes, as well as percent fibrous and fibrofatty volumes) were found to be statistically significant with hsCRP, but less so with LDL. In multivariable logistic regression, existing diabetes and TCFA at baseline, rather than baseline or change in serum biomarkers, demonstrated the strongest associations with the presence of TCFA at follow-up (adjusted OR 3.17, 95% CI 1.62–9.97 for diabetes and adjusted OR 8.82, 95% CI 3.04–27.92 for TCFA at baseline). The authors report that a

Correspondence to Dr. Viviany R. Taqueti, Cardiovascular Imaging Program, Brigham and Women's Hospital, ASB-L1 037-G, 75 Francis Street, Boston, MA 02115, USA. vtaqueti@bwh.harvard.edu tel 1 617 732-6291 fax 1 617 582-6056.

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greater decrease in hsCRP (but not LDLC) was observed in those without, as compared to those with TCFA at follow-up. They cite these data as supportive of the anti-inflammatory effects of statin, specifically on plaque stabilization.

What is new? Using serial IVUS, Nissen et al.[5] previously reported in the multicenter REVERSAL trial (n=502) that patients randomized to intensive atorvastatin (80 mg daily) versus moderate pravastatin (40 mg daily) treatment over 18 months demonstrated reduced progression of coronary atherosclerosis by change in percent atheroma volume. Patients with slower rates of plaque progression demonstrated greater reductions in levels of both LDLC and CRP, even though the correlation between the reduction in LDLC and CRP levels was modest in the cohort as a whole.[6] Additional investigations[7–10] using serial IVUS, including the SATURN trial of patients receiving only high-intensity statin therapy,[10] reported regression of plaque atheroma volume, but results were relatively modest.

As intracoronary imaging evolved, efforts expanded from simply measuring plaque volume using gray-scale IVUS to focusing on candidate markers of plaque stabilization. With the advent of radiofrequency or VH-IVUS, investigators began to correlate certain plaque characteristics at baseline with downstream response to therapy[11, 12] and future cardiovascular events.[13] In the PROSPECT trial, the presence of a TCFA was independently associated with the occurrence of a major adverse cardiovascular event at the site of a previously defined angiographically mild, nonculprit lesion (HR 3.35, 95% CI 1.77–6.36)[13]. The current study adds to the existing literature an analysis of serial VH-IVUS-defined plaque characteristics and serum lipid and inflammatory biomarkers in a cohort of Asian patients on a contemporary statin for secondary prevention.

Care should be taken when making direct comparisons between STABLE and earlier trials such as REVERSAL, which utilized gray-scale IVUS and demonstrated that changes in both hsCRP and LDLC correlate with change in plaque volume. STABLE was a single center experience with smaller sample size and shorter study duration. It is possible that the STABLE trial, despite use of VH-IVUS, was underpowered to detect consistent associations between differences in serum biomarkers and plaque characteristics Relatively low power may also explain why little correlation was observed between serum biomarkers and percent atheroma volume using traditional gray-scale IVUS, and why little difference was observed between high- and low-dose rosuvastatin.

Despite limitations, the current study by Kwon and Kang et al. is important because it ultimately makes the point that the dramatic LDLC and hsCRP lowering seen on average in patients on a later-generation statin (with proven survival benefit in large outcomes trials[2, 14, 15]), is not fully captured using either gray-scale or VH-IVUS evaluation of any given plaque. Indeed, the strongest marker associated with presence of TCFA post-statin in this study was the presence of TCFA at baseline. Even TCFA, which as defined by VH-IVUS has gained popularity as a surrogate for unstable plaque, lacks specificity; of 595 TCFA identified in PROSPECT, only 26 were actually associated with sites of future events over 3 years of follow-up.[13] We must thus acknowledge that the quest for focal endpoint evidence (i.e. at the level of individual plaque anatomy) for what is almost certainly a

systemic biological effect (e.g. the lipid-lowering and anti-inflammatory effects of statins) may never be fully realized.

Recent work has called attention to the fact that patients with “residual inflammatory risk” are biologically distinct from those with “residual cholesterol risk.”[16] In this regard, the current data also underscore the need to separate lipid-lowering from anti-inflammatory effects of atherosclerotic therapies, as is now underway in cardiovascular outcomes trials of anti-inflammatory therapy for secondary prevention.[17–19] Embedded within these trials are innovative imaging substudies utilizing FDG-PET assessment of plaque inflammation to correlate with changes in plaque morphology[20] at the local level, as well as cardiac PET quantification of coronary flow reserve to correlate global vasomotor and microvascular function with cardiac structure[21] and serum biomarkers[22] systemically. When complete, these concomitant imaging and outcome data may help to more precisely phenotype patients with residual risk and to determine best approaches for the care of our patients.

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