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EDITORIAL COMMENT

Plaque Burden With Composition?

That Is the Next Question*

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Atherosclerosis is a chronic systemic disease, frequently leading to vascular morbidity and premature mortality. Although atherosclerosis is systemic, plaque rupture, like politics, is local. The emergence of innovative plaque imaging modalities has fueled interest in identifying features of coronary atherosclerosis most likely to be associated with adverse cardiovascular events. Although several biologically plausible characteristics of coronary plaque have been proposed, none has been linked with either sudden death or nonfatal myocardial infarction (MI). Plaque severity is 1 of several elements that have been studied with intravascular ultrasound (IVUS).

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In this issue of the *Journal*, Hirohata et al. (1) randomized 247 patients with stable angina undergoing percutaneous coronary intervention to either olmesartan or placebo and performed IVUS of a nonculprit coronary artery at baseline and 14 months. Treatment allocation was concealed from the IVUS core laboratory, where coronary arteries were systematically interrogated with standard grayscale IVUS imaging techniques. At baseline, the percent atheroma volume (PAV) was somewhat greater in the olmesartan group (43.8% vs. 40.6%, $p = 0.03$). At 14 months there was significant plaque progression in the control group as measured by total atheroma volume (TAV) (208.8 to 215.9 mm^3) but no change (neither progression nor regression) in the olmesartan group. Mean percent change in TAV was 5.4% in the control group at follow-up, compared with 0.6% in the olmesartan group ($p = 0.016$). Similarly, PAV increased 3.1% in control subjects but declined by 0.7% in the treatment group ($p = 0.038$). These findings suggest a relationship between olmesartan therapy and delayed coronary atheroma progression.

Change in PAV is often the primary efficacy parameter in IVUS studies not because it is associated with major adverse cardiac events (MACE) but rather for its minimal variance and greater statistical power. It is important to note that PAV (Equation 1) is actually a "composite" IVUS measurement, driven by 2 biological processes: 1) change in coronary plaque volume; and 2) magnitude and direction of coronary artery remodeling occurring between baseline and follow-up measurements. Thus PAV does not solely measure changes in plaque volume. By contrast, TAV only measures plaque progression/regression. Although analysis of plaque progression metrics with MACE in ongoing serial IVUS trials is highly anticipated, to date there are no data linking either TAV or PAV with observed MACE.

$$\text{PAV} = \frac{\sum (\text{EEM}_{\text{CSA}} - \text{Lumen}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \times 100 \qquad \text{[Equation 1]}$$

In the present study there was an approximate 3% increase in PAV in the control group and a 0.7% decrease in the olmesartan group. This magnitude of change is consistent with previous IVUS studies. For example, ASTEROID (A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden) investigators (2) performed IVUS in 349 patients who received intensive statin therapy with rosuvastatin. Pre-specified IVUS parameters were PAV and change in TAV in the 10-mm subsegment with the greatest plaque severity. Rosuvastatin was associated with reductions in low-density lipoprotein cholesterol, PAV (−0.98%), and TAV (−6.1 mm^3). ASTEROID demonstrated rosuvastatin was associated with modest numerical but significant plaque regression, as opposed to delayed progression in the present study.

Because no studies to date have directly demonstrated an association between change in PAV and future risk of cardiovascular events, it is of interest to determine whether IVUS findings are concordant with cardiovascular outcomes associated with the studied intervention. As shown in ASTEROID, there was clear concordance between IVUS measures of atherosclerosis and clinical benefit of rosuvastatin. There are 2 notable examples where clear concordance between IVUS surrogates and clinical efficacy of the pharmacotherapy is lacking: 1) recombinant ApoA-I Milano; and 2) cholesterol ester transfer protein inhibition. The effect of intravenous recombinant infusion of ApoA-I Milano (ETC-216) on plaque progression was studied in 57 acute coronary syndromes (ACS) patients (3). The ApoA-I Milano was given shortly after ACS presentation in 5 weekly treatments and was associated with reductions of 1.06% in PAV and 4.2% in TAV compared with baseline. Despite these findings, ApoA-I Milano has not been fully developed, for reasons that are not entirely clear. Demon-

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stration of concordance between IVUS and the clinical efficacy of ApoA-1 Milano might be prolonged, because clinical development stalled shortly after Pfizer (New York, New York) acquired ETC-216 (4). Although retaining intellectual property rights to this compound, Pfizer has divested other significant lipid regulatory molecules, leaving much ambiguity on future clinical development of high-density lipoprotein cholesterol therapies.

Torcetrapib, a cholesterol ester transfer protein inhibitor, was studied in ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) (cardiovascular outcomes) and ILLUSTRATE (Investigation of Lipid Level management using coronary Ultra-Sound To assess Reduction of Atherosclerosis by ceTp inhibition and HDL Elevation) (IVUS) (5). Over 15,000 patients were randomized to torcetrapib or placebo in ILLUMINATE. Although high-density lipoprotein cholesterol levels increased by more than 60% in the torcetrapib arm, the trial was terminated prematurely due to an increased risk of death and cardiac events in these patients. ILLUSTRATE (6) randomized 910 patients to atorvastatin and torcetrapib or atorvastatin monotherapy. Serial IVUS findings showed that PAV increased by 0.19% in the control group and by 0.12% in the combination group ($p = 0.72$). By contrast, there was significant plaque regression in the torcetrapib group as evaluated by a reduction in normalized atheroma volume (-9.5 mm^3 torcetrapib vs. -6.3 mm^3 control, $p = 0.02$). Thus the IVUS findings were not clearly concordant with the safety signal seen in ILLUSTRATE, suggesting that the use of IVUS end points as surrogate markers for atherosclerosis is a complex issue. Certainly, although there was no beneficial effect on PAV, torcetrapib led to plaque regression as measured by atheroma volume. It is possible that off-target effects of torcetrapib might have accounted for the cardiovascular safety signal, but of course IVUS would not be expected to reveal these.

Progression of atherosclerosis has also been evaluated in glucose-lowering treatments. The PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) trial (7) randomized 543 individuals with type 2 diabetes to the maximum tolerated dosage of glimepiride or pioglitazone. Repeat IVUS was available in 360 patients. The main outcome measure, PAV, increased by 0.73% in the glimepiride arm and decreased 0.16% in the pioglitazone arm ($p = 0.002$). Although the cardiovascular effects of glucose-lowering are yet unknown, pioglitazone was associated with a reduction in death and MI in PROactive (PROspective pioglitAzone Clinical Trial In macro-Vascular Events) (8). A recent meta-analysis (9) also suggests improvement in cardiovascular outcomes associated with aggressive treatment. Thus, results from the PERISCOPE trial are mostly concordant with the perceived benefit of pioglitazone on MACE.

The salient issue is whether plaque quantity, composition, eccentricity, vessel remodeling, or a combination of these will be linked with risk for MACE. Innovation in imaging platforms now makes it clinically feasible to identify compositional elements of coronary atherosclerosis. Examples of emerging platforms include optical coherence tomography, near-infrared spectroscopy, and various IVUS platforms, including integrated backscatter, Virtual Histology (VH) (Volcano Corp., Rancho Cordova, California) and wavelet analysis. VH-IVUS uses the mathematical technique of autoregressive modeling to classify IVUS-radiofrequency data into 1 of 4 color-coded plaque components: 1) fibrous (green); 2) fibrofatty (light green); 3) dense calcium (white); and 4) necrotic core (red). Expert consensus guidelines for analyzing and interpreting VH-IVUS images have been published (10). Based on composition analysis, this platform can be extended to define specific plaque phenotypes, including adaptive and pathological intimal thickening, thin cap fibroatheroma (TCFA), fibroatheroma, and fibrocalcific. Of these, TCFA is widely believed to be the leading vulnerable plaque phenotype. Although a consensus description does not yet exist, likely characteristics of VH-TCFA include plaque thickness >600 μm, confluent luminal necrotic core, and no fibrous cap. Although an unresolved issue, linking plaque severity with composition might also add important prognostic information. Thus a minimal plaque burden threshold (approximately 50%) with TCFA is also of interest. Prior IVUS studies have demonstrated symptomatic future plaque rupture to be associated with relatively greater plaque burden and smaller lumen size (11).

Confluent necrotic core is a key element of TCFA and plaque rupture (12). Recent studies have suggested that the quantity of necrotic core might be modifiable with pharmacotherapy. In 330 patients randomized to the lipoprotein-associated phospholipase A2 (Lp-PLA^2) inhibitor darapladib (160 mg daily) or placebo, Serruys et al. (13) found a reduction in necrotic core volume with darapladib at 12 months (-0.5 ± 13.9 mm^3, $p = 0.71$) compared with a significant increase in placebo-treated subjects (4.5 ± 17.9 mm^3, $p = 0.009$). The intergroup difference was -5.2 mm^3, $p = 0.012$. Although TAV decreased in both groups compared with baseline, the difference between groups was not significant. Although they suggest that meaningful changes in composition might occur without measured differences in plaque severity, the clinical utility of these findings is unknown.

Several studies have recently been published that have attempted to link TCFA with cardiovascular risk. An association between the frequency of VH-TCFA and Framingham Risk Score (14) as well as duration of diabetes (15) has been demonstrated, both of which are associated with greater cardiovascular risk. In over 300 ACS and stable angina patients who underwent VH-IVUS, culprit lesions from the ACS cohort were significantly more likely to be VH-TCFA compared with the stable angina cohort (16). Although it should be noted that these cross-sectional studies all fall short in linking TCFA as a potential vulnerable plaque phenotype

with risk of future MACE, the long-awaited results of PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) (17)—recently presented at the Transcatheter Cardiovascular Therapeutics 2009 conference—provide the first insights on atherosclerosis progression and secondary events in an ACS population. The PROSPECT investigators enrolled 697 ACS patients (66% non–ST-segment elevation MI, 30% ST-segment elevation MI, 4% unstable angina) who mostly underwent 3-vessel VH-IVUS at baseline. Imaging studies were repeated over the next 5 years in patients with repeat events. In nearly 2,700 lesions identified at baseline, 13% contained necrotic core and 22.4% were classified as VH-TCFA, defined as >10% necrotic core without a visible fibrous cap at the lumen. During median follow-up of 3.4 years, 11.6% of patients developed MACE involving a nonculprit lesion (the primary end point), although 12.4% had MACE involving a culprit lesion. Lesions classified as VH-TCFA were associated with the greatest risk of MACE in a nonculprit lesion (hazard ratio: 3.84, 95% confidence interval: 2.22 to 6.65, $p < 0.0001$). The VH-TCFA lesions combined with >70% plaque burden were associated with the greatest risk of MACE in a nonculprit lesion (hazard ratio: 10.8, 95% confidence interval: 5.5 to 21.0, $p < 0.0001$). These very preliminary results suggest that grayscale IVUS coupled with compositional analysis might be a powerful tool to localize high-risk regions for future MI. Undoubtedly, there will be interest in plaque-modifying interventions designed to lower individual risk for mortal and morbid cardiovascular events.

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