Patients with diabetes mellitus are at increased risk of death resulting from cardiovascular disease, but the best strategy to control excess cardiovascular risk is not yet clear. Although the use of statins and angiotensin antagonists has been successful, treatment of diabetes mellitus itself, especially from the standpoint of degree of glycemic control and type of antidiabetic agents, remains an area of ongoing investigation. Once touted as having the potential for athero-protection because of their favorable effects on inflammatory biomarkers, endothelial function, carotid intimal-medial thickness, and even macrophage and lipid deposition, the thiazolidinediones (TZD) have become substantially controversial after a meta-analysis suggested an increase in the risk of myocardial infarction in patients treated with rosiglitazone. Although this notion was not confirmed in an interim investigation. Once touted as having the potential for athero-protection because of their favorable effects on inflammatory biomarkers, endothelial function, carotid intimal-medial thickness, and even macrophage and lipid deposition, the thiazolidinediones (TZD) have become substantially controversial after a meta-analysis suggested an increase in the risk of myocardial infarction in patients treated with rosiglitazone. Although this notion was not confirmed in an interim investigation. Once touted as having the potential for athero-protection because of their favorable effects on inflammatory biomarkers, endothelial function, carotid intimal-medial thickness, and even macrophage and lipid deposition, the thiazolidinediones (TZD) have become substantially controversial after a meta-analysis suggested an increase in the risk of myocardial infarction in patients treated with rosiglitazone.

Seeking Alternatives to Hard End Points

Is Imaging the Best APPROACH?

Aloke V. Finn, MD; Y. Chandrashekhar, MD; Jagat Narula, MD, PhD

Do These Results Help Evaluate the Effects of TZD on Atherosclerosis?

Using a similar primary end point, the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial, had compared another TZD with a sulfonylurea, wherein pioglitazone resulted in a lower rate of atherosclerosis progression (\(\Delta PAV -0.16\%\)) in comparison with glimepiride (\(\Delta PAV +0.73\%\)). Although rosiglitazone in APPROACH influenced atheroma progression in a similar manner as pioglitazone in PERISCOPE, progression was somewhat greater in the glimepiride-treated patients than in those treated with glipizide. It is possible that the difference in the sulfonylurea groups could have blunted the significance of rosiglitazone, rather than any major difference in effects of 2 TZDs on atheroma biology. A greater proportion of patients had received insulin in the sulfonylurea group in PERISCOPE (23%) than in APPROACH (9%) and might have contributed to this difference. Insulin-treated diabetic individuals have demonstrated greater PAV than non-insulin-treated patients. This leads one to ponder whether the APPROACH trial might have been favorable for rosiglitazone if the insulin-treated population had been as high as that in PERISCOPE. This is indeed a possibility because plaque progression was seen in the presence of more advanced diabetes mellitus, and secondary IVUS outcomes supported better outcomes in some subgroups. Furthermore, a longer follow-up in such studies could have been interesting. Atheroma plaque volume reduction is a rather slow process, more so than plaque stabilization, with a small percent change in PAV as seen in the previous IVUS studies with lipid-lowering therapy. The landmark A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound–Derived Coronary Atheroma Burden (ASTEROID) trial demonstrated a measurable change after 24 months of follow-up and might explain the dissociation between regression in IVUS studies and event rates in the outcome studies. Magnetic resonance imaging studies in diabetic patients treated with rosiglitazone had failed to show carotid plaque regression at 12 months.

Could there still be a biological explanation for the difference in TZD effects? All agonists of peroxisomal proliferator–activated receptor, a transcription factor expressed in smooth muscle, endothelial cells, and inflammatory cells including macrophages, have complex effects on measures of coronary risk. The TZDs are known to inhibit proliferation of vascular smooth muscle cells through cyclin-
dependent kinase arrest, and this effect probably underlies the efficacy of TZDs both in preventing intimal thickening after stent placement and on carotid artery intima-media thickness. Some TZD effects, such as on low-density lipoprotein cholesterol levels, may not be class effects and could be unique in direction or magnitude, and reinforce the need to evaluate each TZD on its own merits. Whereas rosiglitazone exerted favorable effects on inflammatory mediators of cardiovascular disease risk such as high-sensitivity C-reactive protein and matrix metalloproteinase 9, it significantly increased low-density lipoprotein cholesterol (an effect not limited to APPROACH). Although TZDs promote reverse cholesterol transport from macrophages and retard inflammatory cytokine production, pioglitazone-treated atherosclerotic mice have demonstrated an increase in plaque necrosis and apoptotic cells, which might offset the beneficial effects of insulin sensitization. This introduces more complexity than can be visualized from changes in plaque anatomy alone.

Does This Study Support Imaging for Surrogate End Points?
Atheroma burden is a strong predictor of future events, especially in diabetic individuals, and, not surprisingly, imaging the morphology of the vessel wall with IVUS has been a fruitful area of research. From using IVUS to understand the morphology in atherosclerosis in diabetic individuals, it has been used in the current study as a possible surrogate for future events and a predictor of efficacy of therapy. Although used in multiple studies, this approach raises important questions for investigative strategies. Is the change in plaque volume a good surrogate for future events (the main parameter that the physician and the patient are concerned with), or should we image more than just plaque volume to understand this risk? It is important to recognize that the surrogate primary end points, such as ΔPAV, offer potential in terms of evaluating the progression or regression of atherosclerotic process, and allow for rather smaller clinical trials in comparison with those powered for clinical events. However, convincing evidence that links ΔPAV to change in cardiovascular risk is still lacking, and this makes IVUS-based trials, even if the results are strongly positive, still not entirely conclusive. One could argue that nearly 10 years’ worth of multiple IVUS-based studies have provided important incremental information that, however, has not yet been translated into a robust clinical event or outcome-related correlation. It might thus be time to move on to explore techniques that go beyond IVUS-verified ΔPAV and to establish the relationship between IVUS characteristics and outcomes.

Although atherosclerotic disease often results in flow-limiting lesions, most patients die of an acute coronary syndrome, usually associated with ruptured plaques, rather than progressive stenosis. In that scenario, especially in the absence of an IVUS-related correlation with outcome data, and given that IVUS has not yet been able to clearly identify, a priori, a vulnerable plaque, it might be important to describe plaque components and to define changes in those components with therapy, rather than evaluate plaque volume alone. The APPROACH study did not observe a significant progression of PAV in both the rosiglitazone and the glipizide groups, but the lack of a control group (ethically so) does not allow prediction of how much the plaque would have progressed otherwise. Similar data from other studies, albeit in nondiabetic individuals receiving a less potent statin, showed progression in the 18-month time frame. Thus, the absence of ΔPAV does not automatically indicate that the drug did not mediate a favorable influence on the plaque. A significant reduction in IVUS-verified lipid volume in response to a statin may be accompanied by a corresponding increase in fibrous lesion volume and result in minimal ΔPAV, similar to no ΔPAV in a placebo group. It might, therefore, be valuable to know what changed in the plaque, because attenuating different components might have different consequences. Furthermore, if the lack of progression was mediated via lipid depletion (even in the presence of rosiglitazone-induced increase in low-density lipoprotein), more aggressive lipid-lowering therapy might be indicated. As such, IVUS studies, of the kind reported in recent years, would offer only a coarse lens toward the otherwise dynamic plaque biology. It is of paramount importance that we exploit IVUS (and any of the other future imaging techniques) to help answer more pressing questions, such as: Is there a regression in the lipid core, or is attenuation of progression simply inferior to achieving frank regression? And, more importantly, such studies might allow us to determine whether a morphological change or a lack thereof within the vascular wall is a superior determinant of drug efficacy in comparison with the favorable effects on well-established peripheral markers (eg, low-density lipoprotein)—a la ENHANCE (Effect of Combinational Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial controversy.

What Could Be a More Informative IVUS Imaging of Plaque?
Because of its limited resolution, IVUS is incapable of measuring all the indices of high-risk plaques (Figure). The culprit lesions associated with acute coronary events, on IVUS interrogation, demonstrate hypoechoic, eccentric plaques that are usually free of calcification. These IVUS characteristics, including large and positively remodeled lesions with shallow echoluent cores, observed in nonculprit plaques have been shown to be the precursors of future events. Although the resolution of IVUS (150 to 300 μm) is inadequate to detect fibrous cap attenuation (50 to 75 μm), refinement of the IVUS technology has allowed better demonstration of plaque composition. Radiofrequency signals can be obtained with conventional 40-MHz IVUS catheters, and subsequent integrated backscatter of the radiofrequency signal can be calculated and color coded, providing a quantitative visual readout for lipid-rich, fibrous, and mixed lesion volumes. By use of such a strategy, a significant reduction in lipid volume and corresponding increase in fibrous lesion volume has been demonstrated in response to statins. The change in lipid volume occurred without significant changes in lumen area and diameter stenosis, indicating plaque stabilization and changes in plaque characteristics before geomet-
ric plaque regression. Similarly, wavelet analysis of radiofrequency IVUS signals allows mathematical assessment of focal differences within arterial walls. Color coding of the wavelet correlation coefficient detects changes in the geometric profile of time-series signals to derive an image of plaque components, as validated in necropsy or directional atherectomy specimens. Virtual histology applies spectral analysis of the IVUS backscatter radiofrequency signal to characterize plaque components as calcified, fibrofatty, calcified-necrotic core, and lipid-rich areas. A recently reported large multicenter study, Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT), used IVUS virtual histology to identify morphological characteristics of nonculprit lesions in patients undergoing primary coronary intervention for acute coronary syndromes. These patients were followed up for 3 years after the procedure to identify the predictors of future coronary events related to the originally nonculprit lesions. Baseline clinical and angiographic factors were poor predictors of future events. In multivariable analysis, IVUS-verified large plaque area and shallow necrotic core (presumed to be an indicator of thin cap fibroatheroma) were able to predict the likelihood of future coronary events. It is possible that the use of IVUS to define individual plaque characteristics might hold more promise for cardiovascular risk prediction, especially as the combination of IVUS with optical coherence tomography and near-infrared spectroscopy fibers becomes available.

Although the APPROACH trial adds to the rich body of existing IVUS literature, it also behooves us to build on the usefulness of imaging strategies. If imaging were to be the alternative to the hard end points of acute coronary events, it would be important that investigators identify IVUS-based parameters that are more informative and to define common criteria for the use of these parameters as end points. This will allow better comparability of the data obtained from different trials. Finally, if the rosiglitazone controversy teaches us one thing, it would be an increased respect for primacy of outcome data. All the current and future imaging techniques, while ever increasingly informative, should be vetted, not with their ability to image, but with their ability to predict, and predict the outcome. Nonetheless, as a strong proponent of imaging modalities, we feel elated that the imaging is being increasingly used as the basis of cardiovascular investigation.

**Disclosures**

None.

**References**


**Key Words:** Editorials ■ acute coronary syndrome ■ atherosclerosis ■ coronary disease ■ plaque ■ ultrasonography, interventional
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