Computed Tomography Coronary Plaque Imaging as a Secondary End Point for Randomized Pharmaceutical Trials

More Bang for the Buck?

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In a perfect world for the cardiovascular computed tomography (CT) researcher, quantitative assessment of coronary atherosclerotic plaque using CT angiography (CTA) has been validated as a surrogate end point for major cardiovascular events and is used to prove the efficacy and efficiency of new drugs in a very cost-effective manner within a viable framework provided by the US Food and Drug Administration. Moreover, this validated imaging biomarker would be on its way to being implemented into decision-making by practicing clinicians, and clinical cardiac CTA examinations would be performed and interpreted with adherence to a strict protocol standard.

Now back to reality, despite more than 30 years of use, imaging and cardiovascular imaging have no such wonder to offer. Only tumor size is accepted as the end point in clinical trials, with varying degrees of success. The situation is nearly as frustrating with blood biomarkers, where only cholesterol has the blessing of the Food and Drug Administration. Given the improved baseline medication of patients, proving the efficacy of new antiatherosclerotic therapies has become more challenging, often requiring megatrails and sample size of tens of thousands of patients. From the viewpoint of a pharmaceutical company, a validated surrogate biomarker, whether it be serological or imaging, would provide the possibility to conduct smaller phase II trials before making the decision to fund a larger phase III study. The opportunity to include imaging in such trials would provide a more direct measure of therapeutic efficacy and could serve as a validation step for its ultimate clinical use in monitoring response to therapy.

However, validation and effective use of biomarkers is challenging. In the APPROACH (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History) trial, rosiglitazone increased high-density lipoprotein levels, which should have translated to improved health outcomes but, instead, resulted in more cardiac events. Although this finding may be explained by off-target effects, it could be directly related to the fact that high-density lipoprotein levels in some patients may prevent high-density lipoprotein from unloading cholesterol, leading to a breakdown of the transport of peripheral low-density lipoprotein to the liver. This rather complex assessment of cholesterol metabolism of course would require accurate measurements of local (ie, liver) rather than systemic lipid concentrations. Thus, a deep understanding of the underlying biology is necessary to increase the potential of using biomarkers as surrogate end points.

In the area of cardiovascular and coronary imaging, intravascular ultrasound-based assessment of coronary artery plaque area and volume has been the most promising biomarker for several years. However, after initial promising results, further studies now are needed to determine the effect of the observed changes on clinical outcomes. Similarly, outcome data are lacking for CT-based assessment of plaque, even though we have had the ability to measure coronary artery calcification for quite some time, and numerous studies have established coronary artery calcification as an independent and incremental predictor for cardiac death and myocardial infarction. Interestingly, a smaller trial, the St Francis Heart Study, had to reject the primary hypothesis that coronary artery calcification-based lipid-lowering therapy leads to fewer events.

Circulating Versus Imaging Biomarkers

Although biomarkers rarely serve as primary end points in clinical trials, they now are used more frequently as an early indicator of the potency and mechanism of new drugs in small phase II trials. In this issue of Circulation Imaging, Tardif et al report on the efficacy and safety of VIA-2291, a potent 5-lipoxygenase inhibitor, and its direct effect on leukotriene levels at 12 weeks. Leukotrienes are proinflammatory cytokines thought to promote inflammation and vulnerability within an atherosclerotic plaque. 5-Lipoxygenase is an enzyme in the pathway for biosynthesis of leukotrienes. As secondary end points, high-sensitivity C-reactive protein, a systemic serological biomarker of inflammation, was measured at 12 weeks, and progression of coronary atherosclerotic plaque as a local imaging biomarker was assessed in a subgroup of patients using contrast-enhanced CT angiography at baseline and 24 weeks. High-sensitivity C-reactive protein has been established as a good prognostic marker for...
major adverse cardiac events, and information on systemic inflammation and local plaque appears to be complementary. The motivation to measure high-sensitivity C-reactive protein and plaque in patients after acute coronary syndrome are based on observations that reduced levels of systemic inflammation translate into a reduction in acute coronary syndrome events as seen in large statin trials, such as PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy trial) and A-to-Z (Aggrastat-to-Zocor Trial). It is yet to be fully understood whether systemic inflammation leads the vulnerable plaque to rupture or vice versa or whether the local effect of a ruptured plaque leads to the release and surge of systemic cytokines. It remains unclear whether inflammation is just a bystander or the cause for plaque vulnerability and rupture.

It is important to recognize the fundamental differences between blood and imaging biomarkers. Blood biomarker measurements are easy to obtain but only represent a one-time nonspecific snapshot of the systemic concentration of the biomarker. In contrast, imaging biomarkers are more challenging to measure but yield information of a more-specific local pathomorphology and its potential modification by the investigational drug. As opposed to blood biomarkers levels, which are subject to the fluxes of daily or even hourly variations, imaging biomarkers are less prone to temporal changes. Thus, it is conceivable that the association of an imaging biomarker with health outcomes could provide a much stronger surrogate end point for antiatherosclerotic therapy than a serum biomarker. Key aspects of serial measurements to assess progression and regression include knowledge of the accuracy of the biomarker, the expected effect size of the intervention on its target and the timeline for such an effect, and knowledge of the variability of the biomarker measurement itself.

The central question is that of the trade-off between cost and benefit. Imaging biomarkers have high sensitivity and specificity for the drug-target interaction, but this is achieved at a higher cost, potential loss during follow-up, and some added risk (eg, radiation). In contrast, blood biomarkers are inexpensive, less prone to incomplete follow-up, and pose minimal or no risk to the patient.

**Contrast-Enhanced Coronary CTA for the Assessment of Coronary Atherosclerotic Plaque**

Contrast-enhanced coronary CTA, with its high spatial resolution, has emerged as an alternative to intravascular ultrasound to noninvasively assess the presence and extent of coronary plaque based on its composition. But how do we assess whether coronary CTA is ready to be used to assess progression of coronary artery disease, and, if so, how should such a study be designed?

Few small studies have attempted to measure serial changes of noncalcified plaque, the main target of interest, because it probably harbors plaques that are at increased risk of rupture. In a study of 50 patients followed over a mean period of 17 months, the mean annualized plaque volume of noncalcified plaques in the left main or proximal left anterior descending artery increased by 22% (95% CI, 14.7% to 29.7%) per year. Interestingly, statin therapy had no significant influence on the mean annualized progression of non-calcified plaque volume ($P=0.6$). In another study of 69 patients, using a semiquantitative score based on the presence of noncalcified plaque in 1-mm cross-sections of the left main coronary artery and proximal 40-mm segments of the other coronary vessels, demonstrated a significant relative increase of 41.9% ($P=0.04$) between baseline and 2-year repeat CTA scan. There was good correlation ($r=0.75; P<0.0001$) between the semiquantitative score and plaque volume ($9.7 \pm 11 \pm 8$ cross-sections containing plaque with $100 \pm 77$ to $125 \pm 91$ mm$^3$ at baseline and follow-up). Furthermore, in a small study in which 27 patients underwent serial CTA after 1 year of treatment with low-dose atorvastatin (20 mg), there was a relative 24% reduction in noncalcified mean plaque volume. However, interobserver variability of plaque volume measurement is substantial (>30%) because the accurate segmentation of plaque boundaries against epicardial fat is difficult. Thus, although noncalcified plaque may be an ideal surrogate end point in clinical trials to test the efficacy of novel antithrombotic therapy, few data are available to support such trial design.

Several of these challenges are evident in the study by Tardif et al. From the 191 patients originally enrolled into study, only 88 qualified for the CT substudy. Among those 88 patients, 60 had acceptable image quality at both baseline and 24-week follow-up. Because the authors prospectively defined noncalcified plaque and stenosis as the outcome measures to assess changes in disease progression, they ultimately have only 34 patients (18% of the original population) with serial CT imaging for their analyses. Thus, the benefits of randomization (elimination of confounding) were lost in this subgroup analysis. Perhaps as a result, the volumetric changes in plaque demonstrated a lack of dose response to the drug intervention, with the greatest drug effect on noncalcified plaque volume, mean plaque density, and percentage stenosis observed at 50 mg of VIA-2291 without a gradient response. Would the results have been the same if the follow-up period had been extended to 1 or 2 years as done in previous studies? Moreover, data from the 34 patients were imputed to present results in 60 and 88 patients in post hoc analysis. This technique typically is used if small amounts of data are missing in a large data set but must be applied with caution if the majority of primary data are missing. The authors appropriately concluded that VIA-2291 reduced leukotriene levels, as defined by their primary end point, and may influence atherosclerosis, but a definite answer on the drug’s effect on plaque progression would need further study.

**Establishing Coronary Plaque Imaging as an Imaging Biomarker**

It is clear that systematic evaluation of changes in noncalcified plaque in a multicenter, multivendor setting using standardized assessment (ie, volume change per plaque, per vessel, per patient) would greatly enhance our ability to define an appropriate study design. As outlined previously, the key questions evolve around a trade-off between measurement accuracy and expected changes over time, which would enable exact definition of measurement time points in relation to sample size and the expected effect of the intervention.
A key question is whether such studies should have a noninferiority or a superiority design. Hints are provided by the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, which demonstrated that high-intensity statin therapy using rosuvastatin 40 mg/d over 24 months results in significant regression of atherosclerosis. However, these changes were relatively small (mean change in percent atheroma volume per vessel, −0.98%; P<0.001) and were obtained in a single vessel only. Thus, it remains unclear whether antiatherosclerotic therapy will result in an overall regression or in stabilization of plaque across the coronary artery tree and whether such a change will occur homogenously.

To overcome some of the challenges of the Tardif et al study, future trial design should include more stringent inclusion and exclusion criteria to optimize image quality and maximize the number of participants with presence of quantifiable noncalcified plaque (ie, based on the baseline CT scan result itself). The incentives for designing studies specifically for plaque CT imaging should be significant because downstream costs of clinical trials could be dramatically reduced, for example, as compared with invasive studies using intravascular ultrasound. In addition, the newest CT technology dramatically reduces the risks associated with radiation exposure (<1 millisievert), which would put it way ahead of invasive techniques because of risks associated with radiation exposure (compared with invasive studies using intravascular ultrasound).

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**Disclosures**

None.

**References**


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