

## Predicting the Future Challenges Moving Forward for Arterial Imaging

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Coronary angiography has been the gold standard of coronary artery imaging for more than half a century. Its ability to identify and quantify the extent of obstructive disease has been widely used to characterize the factors that promote the natural history of atherosclerosis and to triage patients to a range of medical and revascularization therapies. However, the fact that conventional angiography simply images the arterial lumen and does not directly visualize the vessel wall has left many wanting to see much more.

### Article see p 172

Technological advances in arterial wall imaging over the course of the last 3 decades have enhanced the ability to visualize the full thickness of the artery wall and specifically the pathologies that lie within. This has generated important insights into the complex relationship between plaque burden and composition, arterial wall remodeling and vascular reactivity, and their potential relationship to the occurrence of adverse cardiovascular events. Many of the most recent developments in imaging have been based on the concept that factors beyond plaque burden are likely to be important determinants of the symptomatic expression of atherosclerotic disease.

One such factor that has stimulated immense interest involves characterization of shear stress patterns within the coronary vasculature. Preclinical studies have demonstrated a predilection for development of atherosclerotic plaque at regions with low levels of shear stress.<sup>1</sup> This has been proposed to result from alterations in localized cell signaling and gene expression, promoting activation of molecular pathways involved in the formation and propagation of atherosclerotic plaque. Elegant hybrid imaging techniques that combine coronary angiography and intravascular ultrasound enables characterization of local shear stress throughout the coronary artery tree. Meticulous studies have translated these preclinical observations to the in vivo setting in humans, reporting a clear relationship between low levels of localized endothelial shear stress (ESS) and both plaque burden and arterial wall remodeling.<sup>2</sup>

These reports have been extended by Stone and colleagues<sup>3</sup> in the current issue of *Circulation*, in which they report the relationship between localized ESS and future cardiovascular events in the PREDICTION study. Five hundred six patients undergoing percutaneous coronary interventions in the setting of hospitalization for an acute coronary syndrome underwent vascular profiling of an average of 2.7 vessels. Approximately three quarters of patients underwent repeat imaging 6 to 10 months later, with nearly complete clinical follow-up of all patients over the next 12 months. The investigators reported that a greater plaque burden at baseline was associated with more disease progression and that both plaque burden and low ESS were associated with reductions in lumen dimensions. Not surprisingly, this translated to these factors being associated with a greater likelihood of developing a clinically relevant reduction in lumen size requiring percutaneous coronary intervention.

The findings of PREDICTION provide a logical extension to the body of evidence that links abnormal patterns of ESS with atherosclerotic plaque progression. However, it is uncertain whether the findings really provide any incremental information above and beyond the relationship established between disease burden and cardiovascular outcome. Autopsy and imaging studies have consistently demonstrated a direct relationship between the burden and progression of atherosclerotic plaque and cardiovascular events.<sup>4–7</sup> Observations from pathology studies demonstrating the predominance of inflamed, lipid-rich, and necrotic plaques at the site of culprit lesions in acute coronary syndromes has stimulated an intensive effort to use a range of imaging techniques exploiting various aspects of atherosclerotic disease beyond plaque size. Although a number of studies suggest a potential association between these features, such as thin cap fibroatheromas<sup>8</sup> and, in this instance, low ESS, and cardiovascular events, none of these reports to date have convincingly demonstrated any incremental information beyond that observed associating plaque burden with adverse outcomes. To do so remains an ongoing challenge in the development of new imaging modalities.

It was of particular interest that the rate of cardiovascular events during the 12-month follow-up period in PREDICTION was low. Only 5 patients experienced either a cardiac death or were found to have a repeat acute coronary syndrome attributed to disease in a nonstented region. A greater number of coronary revascularization events was noted; however, these occurred in the context of a planned follow-up coronary angiogram and therefore were not primarily symptom driven. The relevance of an association primarily between low ESS and many asymptomatic clinical events is uncertain. This low event rate is similar to that observed in a large observational

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registry of patients undergoing radiofrequency evaluation of intravascular ultrasound imaging after an acute coronary syndrome.<sup>8</sup> Whether this reflects use of established medical therapies in these patients, although the administration of statins at hospital discharge in 70% of patients was far from universal, or inclusion of lower-risk patients than originally perceived in these registries, is uncertain. The relative discord between event rates in these observational registries and experience in the real world, in which event rates are higher, remains to be elucidated. It does pose the question whether these registries involve substantial selection bias, with little relevance to the typical experience in clinical practice.

The findings continue to fuel interest in the focal nature of the disease process. The ultimate progression to symptomatic ischemia, whether it results from progressive decreases in lumen dimensions or sudden episodes of plaque rupture, reflects a focal event. Although the greatest benefits of acute therapeutic interventions have primarily resulted from focal improvements in blood flow, the greatest efforts for prevention have largely been derived from use of systemic therapies that target cardiovascular risk factors. There is interest in potential prophylactic measures to treat focal areas deemed to be of potential greatest risk at promoting clinical events; however, this remains highly speculative and untested in the clinical trial era. Even abnormal shear stress is most likely to be treated with use of systemic therapies targeting risk factors such as blood pressure. These findings do continue to highlight the issue of heterogeneity of vascular disease throughout the length of a given vessel. Imaging studies have demonstrated marked variability in terms of plaque burden, composition, vascular reactivity, arterial remodeling, and now ESS. Whether the patient with established macroscopic atherosclerotic disease has any region that is truly normal or simply harbors regions differing in their degree of abnormality remains to be determined. For the time being, it would appear that treatment strategies are similar regardless of these findings.

The ultimate question that continues to remain unanswered is what are the real implications of the evolution of arterial wall imaging? These techniques have each provided important insights into the natural history of atherosclerosis and an understanding of the factors that have either a protective or detrimental influence. However, the more urgent question remains the utility of imaging beyond the research setting. What is its role in clinical practice? Will imaging be used in the clinical setting to guide therapeutic decision making? Will such use have a positive impact on patient outcome, and is it cost-effective? Although some observational studies suggest

that features of more extensive disease are associated with use of more intensive risk factor modification,<sup>9</sup> this has yet to be tested in a large-scale clinical trial. As the field of arterial wall imaging has continued to mature, surely now we have reached the stage where these clinical trials need to occur.

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