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EDITORIAL COMMENT

Using Imaging to Identify the High-Risk Diabetic Patient

Are We Any Closer?*

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The presence of type 2 diabetes mellitus is well-recognized to portend a greater likelihood of adverse cardiovascular events across a wide range of settings. Observations that the cardiovascular risk of patients with diabetes with no clinically manifest coronary disease is equivalent to nondiabetic survivors of myocardial infarction led to increasing support that diabetes was a coronary risk equivalent (1). Accordingly, treatment guidelines for cardiovascular prevention have emphasized the need for more intensive therapy in the diabetic patient. Moreover, clinical trials of novel antiatherosclerotic agents have sought to enrich their cohorts by selectively promoting recruitment of patients with diabetes. However, experience has demonstrated to us that this does not necessarily increase events and we have therefore increasingly recognized that not all diabetics are made the same.

This evolution of thinking with regard to the likely heterogeneity of cardiovascular risk in the patient with diabetes has prompted us to search for effective ways to phenotype individual risk to determine who is most likely to benefit from more intensive intervention. Although review of registries and clinical trials has suggested that the patient with factors such as a longer duration of diabetes, poor control, and concomitant hypertension and renal dysfunction is likely to fare worse (2), there continues to be an interest in developing novel biomarker approaches to aid risk prediction. This is 1 area in which arterial wall imaging presents considerable opportunity, by virtue of the ability to reliably visualize the full extent of atherosclerotic plaque within a range of vascular territories. Technological advances have extended the ability to the extent of atherosclerotic plaque to potentially being able to discriminate individual plaque phenotypes, in terms of both their composition and functionality. This now provides an important tool, with the ability to generate important information linking the underlying biology with the natural history of cardiovascular risk.

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In this issue of *iJACC*, Kedhi et al. (3) report the findings of an analysis of the PROSPECT (Providing Regional Observations Study Predictors of Events in the Coronary Tree) study, in which they compared the relative influence of the presence of a thin-cap fibroatheroma (TCFA) on cardiovascular event rates in patients with diabetes. Patients had undergone 3-vessel radiofrequency intravascular ultrasonography following successful percutaneous coronary intervention (PCI) of angiographic culprit lesions for an acute coronary syndrome and were subsequently followed for 3 years to record cardiovascular events. This approach has the ability to extend imaging beyond gray-scale visualization of the extent of atherosclerotic plaque to create a spectral tissue map, distinguishing fibrous, fibrofatty, necrotic, and calcific components.

Within PROSPECT, the 3-year incidence of major adverse cardiovascular events was predictably greater in patients with diabetes. Of particular interest, the difference was driven by the presence of patients with diabetes with evidence of at least 1 TCFA, lesions defined by the presence of high plaque burden and large necrotic core. In fact, the failure to detect a TCFA

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in a patient with diabetes resulted in event rates that were comparable to that observed in the nondiabetic group. It is important to note that the presence of a nonculprit TCFA identified patients more likely to experience a cardiovascular event, despite a high rate of use of contemporary medical therapies.

These findings add to a growing body of evidence and interest in the concept that atherosclerotic plaque imaging may play an important role in identifying patients who should be treated more intensively. Whether plaque imaging can identify a patient who is more likely to benefit from use of more intensive therapeutic intervention remains to be determined. In theory, such vulnerable lesions should contain more lipidic and inflammatory material and thus be more responsive to use of systemic therapies. The observation that patients with acute coronary syndrome, for example, derive greater benefit from use of medical therapies would suggest that their disease substrate is potentially more modifiable (4). However, the definitive link between imaging findings and this benefit continues to be investigated.

The findings also have implications for invasive treatment of patients with diabetes in the catheterization laboratory. All patients in PROSPECT had undergone PCI in the setting of an acute coronary syndrome with 3-vessel intravascular imaging. The use of imaging at time of invasive coronary catheterization raises the question of whether such lesions would benefit from more localized therapy in the form of further conventional PCI or use of bioabsorbable scaffolds. Prospective clinical trials that demonstrate a clinical benefit from use of such an approach are required before there can be widespread acceptance of these strategies in clinical practice. Given the success of systemic therapies in preventing the majority of clinical events and potential multitude of potentially vulnerable lesions throughout the coronary vasculature, it remains likely that intensification of medical therapies will be a more effective approach to further reducing cardiovascular risk in patients who present with an acute coronary syndrome.

This report adds further to the concept of whether we can detect the vulnerable plaque and if that can predict a greater likelihood of cardiovascular events. Although there has been considerable interest in the importance of the vulnerable plaque, there has been increasing recognition that not all events are precipitated by plaque rupture. Indeed, recent reports emphasize the prevalence of plaque erosion, associated with a different plaque composition and patient demographics, in up to one-third of patients with acute coronary syndrome (5). The observation that acute events can occur with lesions that do not meet the traditional criteria for plaque vulnerability suggests that failing to identify a TCFA on invasive imaging may not necessarily preclude the risk of a subsequent clinical event.

This continues to reinforce that it is the vulnerability of the whole patient, as opposed to individual lesions, which is more likely to be of use in risk prediction and triage of patients to additional interventions. This is particularly important in the setting of community practice, where imaging is performed in a noninvasive fashion across a broad range of risk in our patients. Although computed tomography and coronary calcium each present considerable promise in the information they reveal about patients and appear in observational studies to alter patient management (6), this information is largely based on their ability to simply detect and quantify the extent of atherosclerosis. Whether measures of plaque composition truly provide incremental risk prediction above and beyond plaque burden remains debatable. To what degree this truly influences cardiovascular outcomes remains poorly studied in prospective, randomized clinical trials. The time has come for those trials to provide such data to inform how best to integrate imaging into our practice.

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