Despite continuous improvements in the catheter-based treatment of coronary artery disease (CAD), our field continues to struggle with the concept that percutaneous intervention may not prevent myocardial infarction or death in the stable patient. The main reason behind this controversial but rather accepted statement is that life-threatening coronary events arise most frequently from lesions that escape proper diagnosis and treatment. As a result, our efforts in clinical practice are almost totally consumed by the treatment of lesions that have limited impact on the natural history of atherothrombosis and CAD. Thus, it is imperative to reflect on this paradox, and do something about it. One way to start is to implement some of the knowledge we have acquired pertaining to our understanding of plaque rupture and thrombosis. We all agree that atherothrombosis evolves in clinical practice are almost totally consumed by the treatment of lesions that have limited impact on the natural history of atherothrombosis and CAD. Thus, it is imperative to reflect on this paradox, and do something about it. One way to start is to implement some of the knowledge we have acquired pertaining to our understanding of plaque rupture and thrombosis. We all agree that atherothrombosis evolves from nonobstructive CAD with specific plaque composition and increased macrophage infiltration.6 Adding these 3 characteristics to the American Heart Association definition of fibroatheroma led to the distinction of TCFA as a separate entity.6 Most importantly, the pivotal concept that plaque rupture can only occur on TCFA, immediately indicted the most relevant form of human disease in the history of mankind and gave us a distinct target in the fight against atherothrombosis.

**Imaging TCFA**

Computerized tomography angiography, intravascular ultrasound virtual histology (IVUS-VH), optical coherence tomography, and near-infrared spectroscopy are actively evolving as useful tools for TCFA imaging.7–9 Of these, IVUS-VH has correlated plaque composition with human coronary atherectomy specimens, proximal disease, positive remodeling, and clinical presentation.9 However, considering the axial resolution of 200 μm, IVUS-VH is limited in its ability to identify TCFA. To partially overcome this limitation, the VH-TCFA definition was created: IVUS-VH TCFA are defined by a focal, necrotic core-containing (≥10% of the total plaque area) in direct contact with the lumen, and in the presence of a percent atheroma volume ≤40%.10 We were enabled for the first time to test the hypothesis that IVUS-VH TCFA can lead to atherothrombosis in a prospective way. The next step will be to select a population at increased risk for coronary events, and patients with diabetes mellitus are well suited for this purpose.

**Why Evaluate Patients With Diabetes Mellitus?**

Approximately 150 million people worldwide and 23 million in the United States alone suffer from diabetes, and the incidence is increasing, with an estimated rise of 165% by 2050.11 As a coronary heart disease equivalent, diabetes increases morbidity and mortality of CAD, even in the era of drug-eluting stents.

Pathology studies have shown that diabetic plaques are characterized by a larger necrotic core, greater plaque burden, and increased macrophage infiltration than those observed in nondiabetic patients.12,13 Furthermore, diabetic plaques have increased neovascularization and erythrocyte extravasation,
also known as intraplaque hemorrhage. The process of intraplaque hemorrhage leads to free cholesterol deposition and increased oxidation related to lysis of the erythrocyte membrane and the toxic effects of extracellular lipid. We have also recently learned that the defense mechanism against intraplaque hemorrhage may be genotype dependent. Haptoglobin is the first line of defense against free hemoglobin. Several studies have shown that in the presence of hyperglycemia the haptoglobin 2 phenotype is deleterious, leading to increased reactive oxygen species generation, lipid peroxidation, macrophage infiltration, high-density lipoprotein oxidation, and iron deposition. This phenotype has also been associated with major adverse cardiovascular events in patients with diabetes mellitus.

Additional lines of defense against intraplaque hemorrhage include the macrophage hemoglobin receptor CD163 and the heme oxygenase-1/ferritin pathway.

### Diabetes Duration and TCFA

The study of Lindsey et al in this issue of *Circulation: Cardiovascular Interventions* reports an increased prevalence of VH-TCFA in patients with diabetes duration >10 years. Compared with a control group of patients with diabetes <10-year duration, the investigators identified a 5-fold greater prevalence of VH-TCFA (54% versus 11%) and increased plaque burden. The study applied a more comprehensive histological approach, which evaluated TCFA as an independent variable. The association between VH-TCFA and diabetes duration persisted when diabetes treatment was added as a covariate. As a result, one mechanism responsible for the increased risk of cardiovascular events in long-standing diabetes is now better defined and may be related to TCFA evolving into lesions that cause symptomatic atherothrombosis.

The ability of VH-TCFA to trigger future events in patients with acute coronary syndrome (ACS) was evaluated in the PROSPECT trial. Three-vessel IVUS-VH was performed on nonculprit, nonstenotic lesions. The incidence of VH-TCFA was 52%, similar to the 54% observed in a >10-year diabetes study. This raises the risk level of patients with long-standing diabetes to that of patients with ACS. Most importantly, the 3-year incidence of events varied from 4% to 17% depending on the concomitant presence of increased plaque burden (>70%) and a reduction of the minimal lumen area <4.0 mm². Isolated TCFA had a 4-fold increased relative risk, with an event rate of 4.4%; however, when TCFA is associated with >70% plaque burden, the relative risk increases to 10.77, with an event rate of 15.3%. Finally, when minimal lumen area <4.0 mm² is added to the equation, the relative risk increases further to 10.81, with an event rate of 17.2%. As a result, isolated TCFA by itself is not the highest risk lesion. Only when TCFA is associated with a large plaque burden does it become a high-risk TCFA. Lumen obstruction (minimal lumen area <4.0 mm²) only minimally influences the relative risk to trigger events. This pivotal observation has tremendous clinical implications for performing IVUS-VH, and we should seriously consider welcoming into our catheterization laboratory imaging modalities that help us to identify the new kid on the block—the high-risk TCFA.

### What Is Next?

The novel invasive information obtained from Lindsey et al and the PROSPECT trial provides remarkable information pertaining to the identification of high-risk TCFA before plaque rupture and thrombosis. However, the populations studied were highly selected (diabetes >10 years and ACS) and represent only a minority of the numerator of potential patients with high-risk TCFA. The overwhelming majority of patients presenting with acute myocardial infarction or sudden cardiac death do so as the first manifestation of CAD, without any previous evaluation or treatment. These patients come from the community, where the denominator is much larger. Invasive technology as a preventive tool in these patients is prohibited and may even be harmful. As a result, only noninvasive testing may offer the possibility to diagnose high-risk TCFA in the primary prevention setting. This concept is supported by the recently reported study by Motoyama et al, which included >1000 patients who underwent computed tomography angiography. Two computed tomography features including positive remodeling and low attenuation (“soft”) plaques provided remarkable prediction value, with a 22% risk of developing ACS. One feature alone provided a risk of 11%. On the other hand, the absence of these features provided a strong negative predictive value, with an ACS incidence of 0.5%.

In the secondary prevention setting, rigorous pharmacological therapy has proven to be an excellent choice for patients with CAD, yet even with the best-combined medical therapy, recurrence of cardiovascular events can be as high as 22% at 30 months. Therefore, this unfortunate subgroup of patients demand improved risk stratification and more aggressive therapy. Diabetic patients with >10-year duration harboring large (>70% plaque burden) high-risk TCFA may be considered for percutaneous intervention. A new stent design with self-expanding, ultrathin struts is currently being evaluated in patients with nonobstructive TCFA, with encouraging preliminary results. If proven to be of significant value, this invasive approach may well be considered as a complementary treatment strategy for patients diagnosed with high-risk TCFA by noninvasive methods. Only strict, randomized clinical studies may help us to elucidate this issue.

Although still in its infancy, it is easy to predict that noninvasive and interventional cardiology will devote increased focus to the high-risk TCFA. Our efforts will then be directed toward preventing life-threatening ischemic events, allowing us to finally alter the natural history of atherothrombosis and CAD.

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