Noninvasive Detection of Vulnerable Plaques
Are We There Yet?

We read with great interest the study by Motoyama et al. (1) demonstrating that patients with low-attenuation and positively remodeled plaques—as detected by computed tomography angiography (CTA)—were more likely to suffer from acute coronary syndromes (ACS) during follow-up. A total of 10,037 coronary segments >2 mm in diameter were analyzed in 1,059 patients; after a follow-up >2 years, 15 of these patients suffered ACS. Adverse CTA features (remodelling and/or low attenuation) were powerful predictors of ACS development after adjustment (hazard ratio: 22.8). This study is provocative indeed, considering that, up to now, the diagnosis of vulnerable plaque (VP) (defined as those at higher risk for future rupture/thrombosis) has been elusive (2).

In fact, despite the use of sophisticated and highly accurate intracoronary diagnostic techniques (intravascular ultrasound, virtual histology, elastography, thermography, coronary angioscopy, and optical coherence tomography) the identification of VP has been not only a moving target but also clinically unreliable (2–5). Currently, with invasive techniques, unique insights on plaque characteristics including morphology, composition, physiologic properties, and even measurements of local temperature, macrophage content and fibrous cap thickness can be obtained; yet we cannot accurately predict their prognosis (2–5).

Addressing some methodological issues would be highly appreciated, considering the potential major implications of the present study (1). First, data confirming that the detected ACS were in fact related to the coronary segment presenting adverse CTA features seems crucial. Therefore, electrocardiographic or angiographic findings correlating ACS episodes with the target vessel/lesion would be reassuring. Conversely, if events arose from other coronary segments, the information would be difficult to interpret.

This is particularly worrisome, considering the study definition of ACS (troponin rise was not required) and that up to 651 segments (excluded from CTA analysis) had previous/scheduled coronary interventions. Second, all patients had established or suspected coronary artery disease; however, information on clinical presentation (asymptomatic, stable angina, stabilized unstable angina) would be of relevance to better define the population risk profile. Third, only 45 patients (4.5%) presented plaques with both attenuation and positive remodelling. Nevertheless, in similar patient cohorts, intravascular ultrasound studies frequently detect multiple nonocclusive plaques with low-echogenicity or significant necrotic cores, associated with positive remodelling (2–5). Accordingly, additional explanations on CTA plaque characterization would be of value to reconcile these apparent discordant results. Fourth, up to 22% of patients harboring plaques with both adverse findings suffered ACS; this is a striking figure, considering the relatively low-risk patient population analyzed. Finally, we should keep in mind that ACS emerge from heterogeneous substrates. Erosion of fibrotic plaques, calcified nodules, and intra-plaque hemorrhage are well-recognized underlying substrates of ACS all lacking the distinct morphologic features of thin-cap fibroatheroma (2).

We fully agree with the authors’ suggestion that additional studies are required to demonstrate the value of CTA to identify the “highly elusive” VP. If the value of CTA to accurately identify high-risk plaques is confirmed (possibly with the additional help of systemic biomarkers), the dawn of a new era—namely that of applying aggressive preventive interventions (intensive systemic therapy or intracoronary stenting) to “passivate” these plaques—will undoubtedly begin.

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Reply

We thank Dr. Alfonso for interest in our manuscript and very insightful comments. We agree that feasibility of noninvasive identification of plaques vulnerable to rupture might have significant clinical implications, and clarify here the methodological issues raised. As described in our paper (1), acute coronary syndromes (ACS) included acute myocardial infarction with the elevation of troponin level and unstable angina without troponin elevation. Our report characterized the plaques that resulted in ACS and excluded the lesions already subjected to intervention or those selected for intervention. As noted in the report, 3 patients developed ACS involving the previously treated lesion and were excluded from the
Diastolic Dysfunction in Aortic Stenosis and Arterial Stiffness

I read with interest the recent paper (1) describing increased mortality in asymptomatic patients with at least moderate aortic stenosis (AS) who have an increased valvuloarterial impedance ($Z_{va}$) (total left ventricular [LV] afterload including arterial pressure). Total LV afterload explains 2 common scenarios often encountered in clinical practice, that of severe AS associated with low aortic valve gradient and normal LV systolic function as well as that of symptoms in some patients with moderate AS. The article implies that the phenomenon of low cardiac output is related to increased LV afterload from both AS and systemic arterial hypertension. I would propose another variable that contributes to low cardiac output as well as heart failure symptoms in this cohort, that of ventricular stiffening and diastolic dysfunction. Arterial stiffness is associated with diastolic LV dysfunction (2). Aside from LV afterload, LV pre-load and diastolic filling parameters may contribute significantly to the reduced stroke volume and cardiac output. Enlarged left atrial volume index as well as grade II or greater diastolic dysfunction, indicating compliance abnormality and elevated LV end diastolic pressure may be indicators of diastolic dysfunction in this group. A review of Table 1 in their data (1) shows that diastolic dysfunction prevalence was comparable in patients with the 3 categories of $Z_{va} <3.5$, 3.5 to 4.5, and 4.5 mm Hg/ml. However, the grade of diastolic dysfunction was not quantified or presented. Diastolic dysfunction is expected in this cohort of patients with AS, increased LV mass, hypertension, and mean age of 66 years. However, it is the grade of diastolic dysfunction that may help to determine its potential role in causing reduced LV diastolic volume as well as potentially increased pulmonary venous congestion and elevated pulmonary artery pressure, and in turn, heart failure symptoms. The data on pulmonary artery pressure also are not presented in their report. Table 1 of Hachicha et al. (1) does show reduced diastolic volume (96 ± 25 ml vs. 111 ± 27 ml) in those in the highest $Z_{va}$ versus lowest $Z_{va}$ groups. Although increased relative wall thickness may explain reduced diastolic volume, diastolic dysfunction may be an important contributor. In addition, atrial fibrillation, another common clinical problem in this group of patients, may coexist, further reducing the atrial contribution to cardiac output. It remains unclear from the report whether patients with atrial fibrillation were included. Evaluation of both LV pre-load and afterload, along with hemodynamics of aortic valve obstruction, may be important parameters to evaluate in clinical practice in patients with AS.

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