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 syndrome (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) include 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