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EDITORIAL COMMENT

# Assessment of Coronary Disease Independent of Symptoms

## No Longer Flying Under the Radar…*

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The first atherosclerotic cardiovascular episode is commonly a life-altering event. Not infrequently it might be a terminal event. Due to the proliferation of imaging investigation and the availability of effective risk factor modification strategies, the focus logically should divert to development of clinical algorithms focused on the prevention of the first atherosclerotic event.

The common practice for prevention of atherosclerotic events relies on *patients' symptoms,* such as angina or angina equivalent, as the nodal step for determining the subsequent course of evaluation. Patients with no symptoms are evaluated by atherosclerotic cardiovascular disease (ASCVD) (or similar) risk estimate scores. In contrast, symptomatic patients undergo either functional or anatomical testing to assess for the presence and extent of *obstructive coronary artery disease* (CAD) as the basis of their symptoms. Such determination dictates downstream testing and medical or percutaneous intervention. This widely prevalent paradigm was historically developed based on the tacit perception that the manifestations of CAD and myocardial infarction (MI) arose from obstruction to blood flow and its functional consequence. Lack of functional significance highlights the limitations of noninvasive functional testing, as negative functional testing (or, for that matter, absence of symptoms) would not distinguish between normal coronary arteries and the presence of nonobstructive atherosclerosis. The traditional paradigm, based on the presence or absence of risk factors, obstructive disease, and symptoms, divides patients into the following groups: 1) at-risk patients for primary prevention; 2) stable ischemic heart disease patients; and 3) patients presenting with acute coronary syndrome. Advances in noninvasive imaging technology have contributed immensely to our understanding of the pathophysiology of MI and exposed shortcomings of the conventional paradigm, and we may need to rethink our approach to CAD to prevent the first atherosclerotic event.

First, presence or absence of chest pain (and symptoms in general) is a poor surrogate for predicting the first atherosclerotic event. Symptoms are neither sensitive nor specific for detecting high-risk CAD. In the majority of patients, the first presentation of coronary disease is an acute coronary syndrome or sudden death, and it is obvious that a symptom-triggered approach would not prevent the occurrence of the first atherosclerotic event. Second, it is evident that imaging evidence of subclinical atherosclerosis in asymptomatic patients allows improved risk stratification for future atherosclerotic events above and beyond the traditional risk estimate scores (1). The 5-year follow-up of the SCOT-HEART (Scottish Computed Tomography of the Heart) trial demonstrated that evidence of atherosclerosis by coronary computed tomography angiography (CTA) followed by tweaking the treatment strategy based on the presence or absence of nonobstructive coronary atherosclerosis improved outcomes even among patients with chest pain (2,3). Similarly, a previous subanalysis of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial demonstrated that the event rate in patients with a negative functional test, but without knowledge of atherosclerosis, was significantly higher than the

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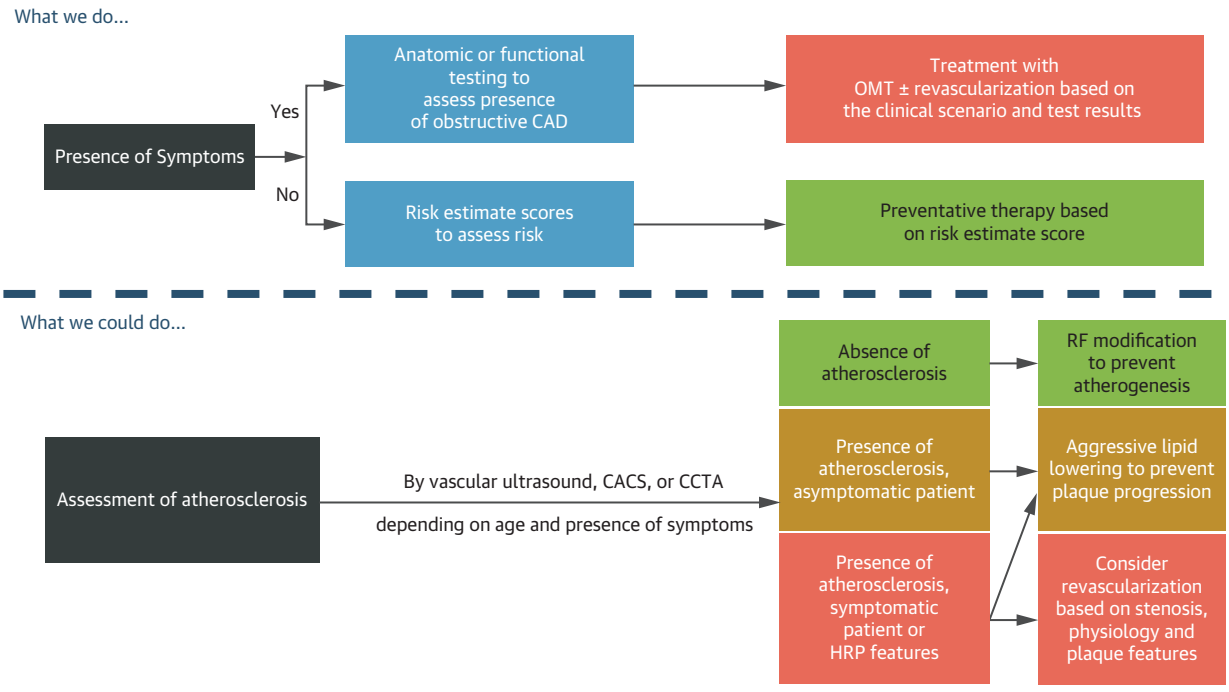
**FIGURE 1 Shifting Perspective in Assessment of Coronary Artery Disease**




CACS = coronary artery calcium score; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; OMT = optimal medical therapy; RF = radiofrequency.

event rate in patients with no coronary CTA evidence of atherosclerosis in the anatomical group (4). The mounting evidence has suggested that the imaging evidence of subclinical atherosclerosis significantly improved risk prediction for the first atherosclerotic event and helped tailor treatment strategies, resulting in superior outcomes. Third, although the absence of imaging evidence of atherosclerosis had an excellent negative predictive value, its positive predictive value can be enhanced by information about the global burden of atherosclerosis, the presence of high-risk plaque (HRP) features, and the rate of plaque progression. Patients with high disease burden, whether obstructive or nonobstructive, demonstrate worse clinical outcomes than patients with lower disease burden (5). Whether the addition of adverse plaque characteristics to the global plaque burden would better the risk stratification has been a subject of debate (6). Although coronary CTA-defined HRP features have been shown to be predictive of events in numerous studies, including subanalyses of the PROMISE and SCOT-HEART trials (7,8), their independent predictive value for future events beyond the global burden of disease has not been convincingly demonstrated in patients with nonobstructive CAD.

In this issue of *iJACC*, Taron et al (9) have provided a *post hoc* analysis of the PROMISE study, focusing on 2,890 patients with chest pain and coronary CTA evidence of *nonobstructive coronary atherosclerosis,* defined as luminal stenosis ranging from 1% to 69%. The composite outcome of unstable angina, MI, and death was independently predicted by ASCVD risk (HR: 1.03; $P = 0.001$); degree of stenosis (30%-69%; HR: 1.91; $P = 0.011$); and presence of ≥2 HRP features (HR: 2.40; $P = 0.008$). Interestingly, the addition of ≥2 HRP features to ASCVD and various markers of global burden of disease, including coronary artery calcium score, segment involvement score, or degree of stenosis, resulted in statistically significant improvement in the model fit.

The study findings are novel and intriguing for 2 main reasons: 1) because in the *absence of significant obstruction* the chest pain is (obviously) not caused by epicardial CAD, it can be concluded that the global burden of disease and the HRP features are predictive of future outcomes, independent of cardiac chest pain; and 2) presence of HRP is predictive of events

above and beyond the global burden of disease, even in the setting of nonobstructive CAD.

The study by Taron et al (9) is thought-provoking and leaves us with more questions than answers. Based on the findings demonstrating the importance of HRP features, even in patients with no obstructive CAD and therefore without epicardial CAD causing chest pain, the following questions (**Figure 1**) should be entertained in the future:

1. Do we even need to evoke chest pain in order to justify noninvasive imaging assessment of coronary atherosclerosis?
2. Knowing that it is the adverse plaque characteristics that ultimately determine the risk of future events and not the presence or absence of chest pain or its typicality, should we start moving away from the historical concept of "stable ischemic heart disease" that is symptom-centered, to "stable atherosclerotic heart disease" that is plaque-centered, for determination of further evaluation and treatment?
3. Do clinical risk scores alone provide sufficient precision to deliver patient-centric prevention of the first atherosclerotic cardiovascular event? How can atherosclerosis imaging supplement and refine clinical risk prediction in an efficient and cost-effective manner?
4. Upon identifying the HRP features in nonobstructive CAD, how can we augment treatment beyond antiplatelet and lipid-lowering therapy? Is there a role for anti-inflammatory therapy in these patients? Is there a role for bioresorbable stents?

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