Progress in multimodality cardiac imaging has relied upon technological advances in providing better accuracy and quantification of the images of interest. Newer-generation cardiovascular diagnostic imaging tools are already equipped with unsurpassed capabilities to integrate a wide range of imaging constructs. This allows the generation of superior characterization of cardiovascular pathology, with the promise to better guide the clinician in deciding the best care for their patients. Although the debate has surrounded which imaging modality (or combination thereof) might provide the best prediction or reclassification of cardiovascular risk, the majority of proposals using existing imaging modalities are still confined to the visual characterization of the cardiovascular structure or function. This is particularly challenging under screening conditions when the lack of clinical manifestations might limit the ability to conduct clinical correlation with the imaging findings.

Several noninvasive strategies have evolved over the years with the hope of better defining future risks of subclinical diseases. Coronary artery calcium (CAC) score is one of more extensively studied screening modalities, providing an integrated quantitative estimate of the degree of atherosclerotic plaque that has progressed to calcification. At present, CAC score is relatively well-accepted in clinical practice as a surrogate for plaque burden, particularly among men and post-menopausal women (1), and has been consistently demonstrated to provide important prognostic value (2). Recent analyses have also confirmed that higher CAC scores might allow reclassification of asymptomatic patients from intermediate- to high-risk categories in up to one-quarter of patients (3). However, the requirement for radiation exposure is an unavoidable limitation for population screening. Questions have also been raised as to whether the presence of calcified plaques correlates with the same culprit lesions that lead to subsequent adverse cardiac events (4). In addition, the presence of calcified plaques might limit the reversal potential of atherosclerotic burden (5), and serial measurements might not directly correlate with treatment responses or outcomes (6,7). Also, CAC score screening did not confer any incremental benefits to treatment guided by stress perfusion imaging (8). Hence, how to best characterize atherosclerosis disease progression once calcified plaques have been identified (i.e., with an intermediate or high CAC score) remains to be determined.

Over the years, there has been an extensive search for ways to characterize vulnerable plaque, particularly related to cell and blood markers of the inflammatory process (9). Myeloperoxidase (MPO) is a leukocyte-derived enzyme that catalyzes the formation of a number of reactive oxidant species and negatively impacts regional nitric oxide levels, leading to increased plaque vulnerability and the development of cardiovascular events (10). Logically, the presence of atherosclerotic plaque should enhance the ability of MPO to provide prognostic value, because MPO itself seems to contribute to processes involved in plaque rupture and intracoronary thrombus generation (11). Being a simple blood test that can be widely available in any standard clinical laboratory, MPO testing might
provide the versatility and the potential clinical utility in serial monitoring of disease progression. Plasma MPO levels show the greatest prognostic value among subjects presenting with a history of chest discomfort or suspect acute coronary syndromes (12–14), and use in risk stratification of higher-risk subjects is the indication for which MPO in vitro diagnostic testing received Food and Drug Administration clearance. However, commercial assays only quantify circulating MPO mass rather than MPO activity in leukocytes, and preanalytical specimen handling and processing are critical to producing accurate results (15). Although some studies have suggested that asymptomatic patients might have similar plasma MPO levels regardless of whether they had underlying coronary artery disease (16), a recent large case control study derived from the EPIC/Norfolk (European Prospective Investigation Into Cancer in Norfolk Prospective Population Study) cohort, a community-based screen of over 25,000 subjects, demonstrated that elevated systemic levels of MPO was associated with increased risk for development of coronary artery disease and mortality risk (17).

It is in the context of combining cardiovascular imaging with a biomarker linked to the pathophysiology of vulnerable plaque that Wong et al. (18) looked beyond traditional imaging techniques. In this issue of iJACC, they report results of a multimodal approach at risk stratification examining the clinical utility of combining the detection of atherosclerotic plaque (indicated by elevated CAC scores) with a marker of the pathogenic process of plaque vulnerability (elevated plasma MPO levels). In a study of over 1,300 individuals, they observed that, compared with those with low CAC scores (0 to 9), those with high CAC score (≥100) had a 19.5-fold risk increase in adverse cardiac events when also presenting with high plasma MPO levels, even after adjusting for clinical covariates. In other words, elevated CAC score clearly serves as a powerful risk stratification tool, but once high CAC scores are observed there is potential for dynamic MPO testing to help gauge who might be at lower risk. Within the cohort examined, a lower plasma MPO level provided some reassurance of a lower rate for cardiovascular events than a high plasma MPO level (7.1% vs. 14.0% at 3.8 years, respectively). To look at this from another angle, for an asymptomatic patient with a detectable high plasma MPO level, a CAC score <100 might provide some reassurance, with cardiovascular risk equivalent to that of low plasma MPO levels. Whether other biomarkers of plaque vulnerability can serve similar complementary prognostic roles will need further investigations (9).

These data might also provide the possibility of instituting more aggressive preventive measures aiming at global cardiovascular risk reduction efforts in those with elevated CAC score and plasma MPO levels. Ideally, we would like to know how to elicit lowering plasma MPO levels, presumably reducing plaque vulnerability. However at present, limited information is available on serial plasma MPO measures in response to various cardiovascular risk-reducing agents. Undoubtedly in the current cost-conscious and risk-adverse environment, there is a need to demonstrate effectiveness of such mechanistic-based multimodality testing in a prospective manner with stringent evaluation criteria (19). This is because even the appropriateness of use for some of the most widely used modalities can be challenged when prospective diagnostic algorithms on at-risk individuals do not produce the intended favorable results (20), and not all mechanism-based interventions can lead to favorable outcomes (21).

Gaining mechanistic insight as part of multimodality imaging might not be a far cry from reality. For example, MPO has become a target for functional imaging of vulnerable plaque and monitoring vascular inflammation, such as within ischemic stroke (22). Direct imaging of MPO activity via an activatable magnetic probe and cardiac magnetic resonance has also been used to monitor in real time a healing myocardial infarction of an ischemia-perfusion animal model, providing a direct visual demonstration of the mechanistic link between MPO expression and both the progression of vulnerable plaque and the involvement of MPO in adverse ventricular remodeling (23). Although the technology of MPO functional imaging is in its infancy and we still cannot adequately visualize the vulnerable plaque, combining diagnostic MPO testing with CAC imaging as a risk stratification approach seems to be an attractive and powerful option with immediate applicability in clinical practice. We definitely need further investigations to refine how to best use imaging modalities in combination with biomarker testing as multimodal risk assessment so that we might better apply preventive measures and fulfill the promise of monitoring those that are vulnerable to cardiovascular events.

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