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iVIEW

EDITOR'S PAGE

Can Biomarkers of Myocardial Injury Provide Complementary Information to Coronary Imaging?

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The number of cardiovascular imaging tools available to cardiologists and scientists have grown exponentially over the past several decades, with innumerable possibilities to measure coronary blood flow, myocardial perfusion, and epicardial atherosclerosis, to name a few. From the perspective of imagers, it seems that all you need is one of an array of imaging modalities and nothing more. However, imaging of cardiovascular structures or functional parameters does not measure many parameters that mediate risk and outcomes, such as inflammation, stress, and subclinical injury, which may be best detected through markers released in the blood. Although an imaging parameter may serve as a surrogate for given blood biomarker, it is in reality one portion of the patient's health that must often be combined with other data for comprehensive diagnosis and risk assessment. Optimally, we must understand both the additive and interactive nature of blood and imaging data to formulate improved patient care strategies. The future might interpret multimodality testing in a more expansive way, referring to multimarker testing rather than just imaging using multiple modalities.

One of the biggest areas of testing is detecting flow-limiting coronary artery disease (CAD) in patients with undifferentiated chest pain and defining their risk for hard events. Although "significant CAD" was the focus for a long time, more recent data suggest a need to look at more than stenosis alone; there are data indicating that flow, resistance, plaque, and the effect of plaque on flow might all be critical, especially when one is looking to interdict adverse future outcomes rather than treat angina alone. Some nonimaging markers, such as high-sensitivity troponin I (hsTnI), identify risk in patients with acute coronary syndromes as well as those presenting with stable chest pain (1,2) or even those without any angina. Would combining imaging with a blood-based marker such as hsTnI of risk be advantageous?

In this issue of *iJACC*, Januzzi et al. (3) provide a secondary analysis from the National Heart, Lung, and Blood Institute–sponsored PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial on the relationship between hsTnI and obstructive CAD in 1,844 patients with chest pain in stable condition randomized to the computed tomographic angiography (CTA) arm of the trial. They hypothesized that hsTnI would detect and quantify the severity of CAD but found that although nearly every patient had measurable hsTnI levels (with 6% having values in the significant range for myocardial injury), and although hsTnI correlated with CAD and coronary

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artery calcification (CAC), it did not perform optimally for diagnostic use. Lower concentrations had negative predictive value nearing 90%, but no hsTnI concentration was able to rule in or rule out CAD adequately.

Why did we as editors find value in this negative study? We have said before that we are not averse to publishing negative studies if they improve understanding of a disease or suggest future strategies. It is clear that troponin elevation predicts adverse cardiac events in acute coronary syndromes as well as stable CAD; in fact, elevations are undesirable even in those without known CAD. In symptomatic outpatients with suspected CAD, higher concentrations of hsTnI even within the normal range portend higher near-term risk for hard events (1). What is not clear if this was related to significantly more CAD in such patients, and some previous studies did not include angiographic assessment of anatomy to prove or disprove this (2). The present study (3) included CTA to confirm CAD and suggests that it is not the case: although there was a gradient of increasing CAD with higher tertiles of hsTnI, the difference was modest (obstructive CAD ranged from 19% in the lowest tertile to 30% in the highest quartile), albeit in a population with very low prevalence of obstructive CAD to start with (12%). However, even with the limited utility of hsTnI for diagnosing CAD, it still might have a role in predicting prognosis. There is already evidence that a biologic marker of plaque might be better than testing for stenosis alone in predicting future risk for events (4). High-risk plaque portends worse fractional flow reserve (5), lower hyperemic blood flow (6), and worse outcomes (7), as well as greater predilection for acute coronary syndromes in the future (8), over and above the effect of stenosis. It is possible that high-risk plaque might also be associated with more troponin leak possibly through subclinical microemboli into the microvasculature or other as yet unknown mechanisms to explain some of these adverse effects; indeed, hsTnI concentrations predict more high-risk plaque as well as greater major adverse cardiovascular events over follow-up (9).

Combining multiple imaging methods or hybrid imaging has shown only modest utility (10), and combining an imaging marker of atheroma such as CAC with a biomarker of risk such as hsTnI may allow us to identify risk better than testing for flow-limiting stenosis alone. This might be a fertile area for future investigation. Other studies have looked at combining imaging with biomarkers with some interesting results (11,12), and this is an emerging field that is likely to expand our ability to diagnose and treat in the future. Identification of CAC increases the use of preventive therapies (13), and acting on such risk marker information modifies risk (14); use of hsTnI may also play a similar role in this regard. CAC has little correlation with numerous other markers (15), and hence combining the two might be of significant utility.

One possibility for application of the PROMISE findings is that we could identify a simple-to-use blood assay to serve as a gatekeeper for the selective use of CAD imaging. Using such a strategy, a patient may present to his or her primary care physician and undergo prompt screening for the detection of elevations in high-sensitivity troponin. Similar to accelerated diagnostic protocols in the emergency department, selective testing could possibly be limited to patients exceeding the threshold value for a given laboratory biomarker, such as high-sensitivity troponin. Indeed, sex-specific thresholds (lower in women to rule out CAD and higher in men to rule in CAD) have been proposed (2). It is interesting to note that the lowest hsTnI levels in this study had very high negative predictive value. In this scenario, reimbursement is relatively inexpensive for troponin assays (the 2017 reimbursement range was ~$29 to $46) and decidedly less than for CTA, thus resulting in sizable cost savings (16). Such tiered strategies are increasingly adopted, for example in the CRESCENT (Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease) trial, in which CAC scoring was used as the gatekeeper for the selective use of CTA, which in turn was used to triage for CT perfusion in symptomatic patients (17). From the present analysis, one may envision that if CTA were limited only to those with a sex-specific threshold for elevated hsTnI, sizable cost savings could be achieved (compared with direct CTA for all symptomatic patients). In this era when lower and lower risk patients are tested, there is increasing interest in the use of a lower cost alternative approach that enriches the yield of secondary testing in higher risk patients. Future research studies looking at the interaction between hsTnI and CTA risk markers (e.g., CAC and measures of nonobstructive atherosclerosis) to predict hard events might have more value than just chasing a paradigm that just looks for flow-limiting stenosis.

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