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EDITORIAL COMMENT

Biomarkers and Imaging in Chest Pain

The Iceberg Beneath the Waterline*

Kavitha Chinnaiyan, MD,[a] James L. Januzzi, Jr, MD[b]

Acute chest pain (ACP) continues to occupy the top tier of symptoms that concern the emergency department physician and the cardiologist. In the preceding decades, ACP has driven much of the field in the quest for the perfect test—one that enables accurate and efficient prediction of not just the need for immediate intervention, but also of subsequent outcomes.

Innovations in the parallel streams of biomarkers and imaging have resulted in an array of testing choices that have enabled an acceleration of ACP triage. The days of prolonged observation are over, replaced by the era of near-immediate testing and triage for coronary artery disease (CAD). With ACP landing anywhere on the spectrum of non-cardiovascular discomfort to acute plaque erosion, rupture, or complete artery occlusion, it is no longer enough to identify coronary stenosis presence or severity. The important question we seek to answer is whether the ACP is the result of *functional* CAD, implying flow limitation or high-risk, unstable plaque. Although biomarkers and imaging have developed in somewhat separate spheres, they are often combined in clinical decision-making and provide complementary information: an abnormal biomarker reflects abnormal biological processes such as myocardial injury or stress that may be confirmed on imaging; alternatively, a significant finding on imaging clues us in to biological changes indicated by biomarkers. Ideally, combining biomarkers and imaging can determine what matters the most, find which is the need for urgent revascularization, and predict hard events.

In the biomarker sphere, high-sensitivity cardiac troponin (hs-cTn) is useful to determine the need for emergent intervention and to predict long-term risk not only in ACP but also in chronic coronary syndromes and heart failure, and even in those without symptoms of coronary ischemia (1). Although the growing body of data on the use of hs-cTn assays has changed the landscape of ACP evaluation, the remarkable strength of troponin assays is also its weakness: clinicians often trust the sensitivity of these tests, frequently considering patients in the "normal range" of hs-cTn as a homogenous, lower risk group, when in truth a wide range of risk exists among those with "normal" troponin, including many with obstructive CAD. Notably, hs-cTn may provide some guidance for understanding the likelihood for CAD presence in those with ACP but without acute myocardial infarction: using hs-cTn, patients may, in fact, be stratified for their risk of obstructive CAD across the normal reference range; such CAD could affect longer-term outcomes (1). Thus, although excluding acute myocardial infarction, one might leverage the information from an hs-cTn in the normal range for further decision making beyond simple discharge. This is where the intersection of markers and imaging might be robust.

In the anatomic imaging sphere, coronary computed tomography angiography (CTA) is an excellent tool in ACP as well as chronic coronary syndromes because of its ability to effectively and safely rule out significant CAD and predict longer-term outcomes. The speed of testing with CTA is associated with lower hospital length of stay and overall costs of care in ACP. Like hs-cTn, the strength

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From the [a]Department of Cardiovascular Medicine, Beaumont Health, Royal Oak, Michigan, USA; and the [b]Cardiology Division, Massachusetts General Hospital, Baim Institute for Clinical Research, Boston, Massachusetts, USA.

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of CTA lies in its very high sensitivity and negative predictive value, which make it an effective "rule out" tool in ACP. Although CTA has provided a rapid triage pathway compared with usual care in the pre-high-sensitivity troponin era, its role has changed considerably in institutions that employ both (2). An advantage of anatomic testing is that it gives a bird's-eye view of the overall burden of CAD, regardless of presence of an acute myocardial infarction—thus, imaging may identify those with unstable angina pectoris as well as those with non-obstructive CAD in whom future interventions for secondary prevention might be of value. Taken together, in ACP, troponin assays could function as gatekeepers to anatomic testing, and considering the combined strengths of high-sensitivity troponin I and CTA, it would make clinical sense to use them together for risk stratification and prognostication that is actionable.

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In this issue of the *Journal*, Lee et al (3) present an analysis of the prospective PRECISE-CTCA (Troponin Within the Normal Reference Range to Risk Stratify Patients with Acute Chest Pain for Computed Tomography Coronary Angiography) trial that enrolled 250 patients in whom an acute myocardial infarction had been excluded through hs-cTnI results below the 99th percentile value. The study participants were stratified into an intermediate range (5 ng/L to sex-specific 99th percentile threshold) and low range (<5 ng/L); the threshold of 5 ng/L was derived by a previous validation study with a negative predictive value >99.5% for acute myocardial infarction or death at 30 days (4). All patients underwent CTA as outpatients after the index hospitalization.

Several important and interesting findings were noted in this study. Patients in the normal but intermediate hs-cTnI group had higher TIMI (Thrombolysis In Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) risk scores at index presentation, higher atherosclerotic burden, and higher probability of more severe CAD. In fact, patients with obstructive and nonobstructive CAD had higher median hs-cTnI concentration than those with normal coronaries on CTA. Importantly, referring physicians and patients were subsequently contacted with recommendations for secondary prevention. It is tempting to speculate that this approach—to identify higher-risk individuals who might otherwise have been discharged home without cardiovascular follow-up and intervene to lower their future risk—might be an important new paradigm of care.

There are several limitations to this study, the lack of clinical outcomes being the most important. Although we await more data on the impact of these findings on hard events, we can assume that a greater burden of CAD portends worse outcomes as previously demonstrated (5), and better recognition and treatment of higher-risk patients would be expected to afford greater ability to treat with greater precision. In light of the quest to determine *functional* CAD, neither plaque characterization data nor physiological assessment with computed tomography-derived fractional flow reserve or computed tomography perfusion, both of which add prognostic value to CTA alone, were reported in the present analysis. In an elegant study from the ROMICAT II (Rule Out Myocardial Infarction/Ischemia using Computer Assisted Tomography) trial, Ferencik et al (6) revealed the incremental value of plaque analysis in predicting acute coronary syndromes in patients with intermediate hs-cTnI levels. Further, abnormal computed tomography-derived fractional flow reserve was associated with ACS, high-risk plaque, and coronary revascularization (7).

Although the association between CAD and intermediate hs-cTn levels is not entirely unexpected, these data add to the ACP triage framework in the era of rapid testing and understanding that an hs-cTn threshold for ruling out an acute ischemic episode may be the tip of the iceberg, while information gained from those with "normal" hs-cTn might better inform the massive iceberg under the waterline when it comes to the burden of CAD. Combining tests judiciously may allow us to be in the unique position of having our cake and eating it too, where safe triage of ACP with a *sensitive biomarker* is combined with preventive therapy for CAD detected by a *sensitive imaging* test.

As every clinician knows, there is not 1 perfect test, and the art of medicine requires balancing the most effective combination of investigations. Instead of focusing entirely on the "rule-out" threshold of high-sensitivity troponin, perhaps the time has come to consider the actual troponin values in an individual patient to determine the need for additional testing with CTA.

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ADDRESS FOR CORRESPONDENCE: Dr Kavitha Chinnaiyan, Beaumont Health, 3601 West 13 Mile Road, Royal Oak, Michigan 48073, USA. E-mail: kavitha.chinnaiyan@beaumont.org. Twitter: @ChinnaiyanMD, @JJHeart_doc.

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