

The sensitivity versus specificity trade-off



Michael Marber, PhD, FRCP
Department of Cardiology, Cardiovascular Division, The Rayne Institute,
St Thomas' Hospital, London, UK

Correspondence: Professor Michael Marber, Department of Cardiology,
Cardiovascular Division, The Rayne Institute, St Thomas' Hospital, Lambeth Palace Road,
London SE1 7EH, United Kingdom
E-mail: mike.marber@kcl.ac.uk

This issue of *Heart and Metabolism* is dedicated to the use of biomarkers in defining risk in acute coronary syndromes (ACS). Although superficially simple, I find this a complex topic dominated by the increasing sensitivity of the cardiac troponin (cTn) assays. The first task is to define ACS and risk.

Evolving myocardial infarction (MI) is of most concern in a patient presenting with chest discomfort and a suspected ACS event. When the presenting electrocardiogram displays diagnostic criteria for ST-segment elevation, biomarkers are irrelevant in guiding immediate management. Thus, the predominant use of biomarkers is in the triage of patients with a suspected ACS event, but without ST-segment elevation on presentation, so-called NSTEMI-ACS. Only about 10% of patients presenting with suspected NSTEMI-ACS end up with a diagnosis of acute myocardial infarction (AMI). This diagnosis is made using standard criteria based on a rise or a fall in a marker of myocardial necrosis, preferably troponin. The historical journey in AMI diagnosis is charted in the Refresher Corner article within this issue by Eggers. From this, it is clear why the troponins are now the favored markers to diagnose AMI among those presenting with suspected NSTEMI-ACS. However, as emphasized by Eggers, problems exist, leaving room for improvement.

The cardiac-restricted troponin isoforms (cTnT and cTnI) are released slowly after myocardial injury, reaching their peak concentration after about 18 hours.¹ To address this biological handicap, the cTn assay vendors increased the analytic performance of their platforms to reliably measure progressively lower

concentrations of cTn. The drive for these innovations was earlier rule in and rule out of AMI. Consequently, there are now at least two commercially available assays that are recognized (by England's National Institute for Health and Clinical Excellence [NICE] and others) to reliably measure cTn concentrations at the 99th centile of a "normal" population—so-called high-sensitivity assays (hsTn). With the advent of hsTn, it has become clear that many patients with cardiovascular risk factors and/or underlying cardiac disease have cTn concentrations above the 99th centile in the absence of an acute event. These "chronic" elevations in cTn have a prevalence as high as 50% in those with underlying chronic heart disease.² The problem is that these are also the very patients who are at increased risk of AMI. It would therefore seem fairly obvious that when cTn concentration cutoffs are defined by the 99th centile of a healthy population, specificity will suffer.³ This is indeed the case, since when the assays are used in this way—as recommended by the American Heart Association, American College of Cardiology, European Society of Cardiology, and now NICE—specificity at presentation for AMI is below 50%.⁴ This conundrum has been nicely summarized by Robert Jesse in commenting that "when troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test."⁵

In addition to poor specificity, the hsTn assays are also not as sensitive as initially hoped, since they are limited by the slow release of troponin. Consequently, up to 23% of patients with a final diagnosis of AMI have a cTn value below the 99th centile at presen-

tation.⁶ The limited sensitivity of the hsTn assays for early diagnosis of AMI has resulted in the current NICE consultation process recommending patients are only discharged from the emergency department if hsTn is below the 99th centile on two blood draws separated by at least three hours.⁷ From the synopsis above, it is clear that new biomarkers are needed and that this issue of *Heart and Metabolism* is timely in addressing many of the deficiencies summarized above.

The article by Wollert provides an excellent and logical background to the biomarker field and highlights that although clinical practice is dominated by necrosis markers, there are many other biomarkers of noncardiac origin that can be used as an index of risk at presentation. The difficulty with these markers is that their specificity for AMI is low. Consequently, clinicians are faced with an even greater quandary than that caused by chronic elevations in hsTn: a patient at high risk, but with no clear strategy available by which to reduce this risk. Once again, that is the advantage of troponin, since at least we know what to do with a rise or fall in cTn indicating AMI, or do we?

The article by Bekkers et al tackles the question of diagnostic changes in cTn indicative of AMI, but with no culprit lesion in a coronary artery apparent on angiography. MI with nonobstructed (<50% stenosis) coronary arteries (MINOCA) is increasing in prevalence as a result of the hsTn assays. What is clear from this article is that cardiac magnetic resonance imaging is the favored gateway investigation to sift through the extensive list of potential differential diagnoses. This is beautifully illustrated and cogently argued within this article, and further reinforced by the Case Report by Maznyczka et al, which highlights that even when coronary artery disease is present, alternative diagnoses for a rise and fall in hsTn still need to be considered.

Given all these problems with hsTn, we begin to question its value in triage of suspected NSTEMI-ACS. This heretical question is tackled head on in the article by Love et al, who highlight that the improved analytic performance of the contemporary cTn assays translates into better diagnostic performance. At this point, going back to a time of more “primitive” assays is out of the question. They make the valid argument that specificity will be improved once serial measurements of cTn become commonplace and we have set criteria as to what constitutes a significant/patho-

logical magnitude of variation between cTn concentrations on separate blood draws. What still needs to be determined are the standardized time intervals between blood draws and the threshold(s) for the delta change.

Finally, we get a glimpse into a future where we may be able to predict plaque rupture events before they have caused myocardial necrosis. The article by Baig et al discusses the nonprotein, small molecule markers of cardiovascular risk and plaque instability that can be detected using mass spectrometry or nuclear magnetic resonance spectroscopy. Although these techniques are not yet clinically applicable to patients at risk of NSTEMI-ACS, they may in the future allow individuals to be profiled and treatments to be tailored and personalized. This is a theme revisited in the Hot Topics article by Huqi, where the case is made for a more global view of the patient, including measurements of inflammation within their vasculature. This holistic view, where every patient is an individual rather than a member of a cohort meeting the entry criteria of a megatrial, is where the art of future medical practice lies. In reaching our ultimate goal of providing personalized care, biomarkers will be even more crucial. ■

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