Troponin in ACS
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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 NSTE-ACS. Only about 10% of patients presenting with suspected NSTE-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 NSTE-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. 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. 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. 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%. 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.”

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-
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. 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 NSTE-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/pathological 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 NSTE-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.

REFERENCES

Using biomarkers to obtain mechanistic insight and guide management in acute coronary syndrome

Kai C. Wollert, MD
Division of Molecular and Translational Cardiology, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

Correspondence: Kai C. Wollert, Hans Borst Center for Heart and Stem Cell Research, Hannover Medical School, 30625 Hannover, Germany
E-mail: wollert.kai@mh-hannover.de

Abstract
Patients presenting with symptoms suggestive of an acute coronary syndrome (ACS) are heterogeneous in terms of their clinical background, preexisting cardiovascular disease, comorbidities, and risk of adverse outcomes. Despite this clinical diversity, cardiac troponin is the only biomarker that is routinely measured in ACS. Conceptually, testing for additional biomarkers may provide mechanistic insight and enable more personalized and more effective management decisions. Most nontroponin biomarkers are produced in multiple tissues, in response to multiple stressors, and in acute as well as in chronic disease states. The information provided by circulating biomarkers is therefore complex and not related to single disease pathways. Nonetheless, several potential indications for nontroponin biomarkers are emerging, where they may be used in a pragmatic fashion for diagnosis, risk stratification, and therapeutic decision making in ACS. ■ Heart Metab. 2015;67:4-8

Keywords: acute coronary syndrome; acute myocardial infarction; biomarker; cardiac troponin; diagnosis; patient management; prognosis

Diagnosis, risk stratification, and therapeutic decision making in ACS
Patients presenting with symptoms suggestive of an acute coronary syndrome (ACS) are heterogeneous in terms of their clinical background, preexisting cardiovascular disease, comorbidities, and risks of ischemic complications, heart failure, or death. In many patients with an initial suspicion of ACS, the diagnosis will eventually be ruled out, and the patients will be found to have other cardiac or noncardiac diagnoses. Patients with suspected ACS therefore constitute a diagnostic, prognostic, and therapeutic challenge. The purpose of early triage is the rapid diagnosis of acute myocardial infarction (MI) and the identification of other urgent conditions. The diagnosis of acute MI is based on the presence of ischemic symptoms, electrocardiogram (ECG) findings, and the documentation of a concentration rise and/or fall of a circulating biomarker of cardiac necrosis. Cardiac troponin (cTn) T or cTnI, measured serially with high-sensitivity as-
Using biomarkers to obtain mechanistic insight and guide management in ACS

Information provided by biomarkers is complex and not related to single disease pathways

Currently, cTn is the only biomarker recommended for diagnosis, risk stratification, and therapeutic decision making in ACS. However, there is a continued interest in using additional circulating biomarkers to obtain mechanistic insight and to further improve the management of patients with ACS. A large number of protein and peptide biomarkers reflecting different pathophysiological mechanisms have been investigated (examples are highlighted in Table I). While the categorization of biomarkers into distinct pathophysiological classes provides a conceptual framework, it is also an oversimplification. Most noncTn biomarkers are produced in multiple tissues and in response to multiple stressors, and virtually all biomarkers integrate information from different disease pathways. Moreover, it can be difficult to distinguish between acute biomarker elevations caused by the ACS and chronic elevations related to underlying cardiovascular and noncardiovascular disease, situations that may require different therapeutic responses (eg, inflammation or matrix remodeling related to chronic atherosclerosis and/or heart failure vs an acute plaque rupture/erosion event and/or infarct healing). In addition, biomarker concentrations are not only determined by their synthesis and release, but also by their catabolism and clearance. As an example, elevated cTn levels reflect not only ischemic and nonischemic cardiomyocyte necrosis, but are also related to ventricular strain, hypertrophy, and failure (similar to the natriuretic peptides), inflammation (eg, elevated levels in sepsis), and renal dysfunction (reduced clearance). Interpretation of cTn levels in patients with suspected ACS therefore requires careful consideration of the clinical context and serial measurements to distinguish acute from chronic and ischemic from nonischemic elevations.

More recently, circulating microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and metabolites have been added to the growing list of potential ACS biomarkers. miRNAs are short noncoding RNA species that function in posttranscriptional regulation of gene expression. miRNAs may circulate in plasma and exhibit remarkable stability to degradation. Based on their tissue selectivity, cardiomyocyte-enriched miRNAs have been proposed as potential diagnostic markers for acute MI. However, a recent study tempered speculations about the usefulness of cardiomyocyte-enriched miRNAs as diagnostic or prognostic markers in ACS. lncRNAs constitute a novel class of RNAs that regulate gene expression and protein function. Unlike miRNAs, plasma concentrations of lncRNAs are very low. A recent study quantified five lncRNA species in blood leukocytes in patients with acute MI. Although four lncRNA species were differentially expressed in patients, there was a large overlap between patients and controls, and none of the investigated lncRNAs emerged as a promising diagnostic biomarker. Since humans express >95 000 different lncRNAs, more promising lncRNA biomark-
Biomarker applications in ACS

Using serial cTn measurements with high-sensitivity assays, the diagnosis of acute MI can be ruled out or ruled in, in most patients within 3 hours, or maybe even within 1 hour, from initial presentation. Recent studies indicate that it may be safe to more rapidly discharge low-to-intermediate risk patients with suspected ACS based on a single measurement of high-sensitivity cTnT and copeptin or heart-type fatty acid-binding protein (h-FABP) on admission. If confirmed in prospective, interventional studies, these biomarker-guided strategies have the potential to further shorten the length of stay in the emergency department in low risk patients without ACS.

Management decisions in NSTE-ACS should be based on a rapid and accurate assessment of risk. Physicians relying on a “subjective” assessment of risk may fail to consider important prognostic factors, and physicians’ underestimation of risk may result in high-risk patients paradoxically receiving less intensive therapies. The European Society of Cardiology (ESC) guidelines therefore recommend a standardized approach that uses the Global Registry of Acute Coronary Events (GRACE) score to calculate risk and guide management decisions. All biomarkers listed in Table I have been related to an adverse prognosis in NSTE-ACS. However, the incremental information provided by these biomarkers beyond the GRACE score and high-sensitivity cTn, information that is already available in all patients as part of routine care, varies considerably. In a recent head-to-head comparison of nine circulating biomarkers, growth differentiation factor 15 (GDF-15) and, to a

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Biomarker characteristics</th>
<th>Primary disease pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTn</td>
<td>Cardiomyocyte-specific protein released upon myocyte strain and cell death</td>
<td>Cardiomyocyte injury</td>
</tr>
<tr>
<td>BNP, NT-proBNP</td>
<td>Peptides released upon ventricular strain, ischemia, and hypertrophy</td>
<td>Ventricular strain</td>
</tr>
<tr>
<td>Copeptin</td>
<td>Peptide released together with the neurohypophysial hormone vasopressin</td>
<td>Hemodynamic stress, osmotic stress</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Ubiquitously expressed protease inhibitor and marker of renal dysfunction</td>
<td>Renal dysfunction, inflammation</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>Widely expressed, pleiotropic carbohydrate-binding protein</td>
<td>Inflammation, wound repair</td>
</tr>
<tr>
<td>GDF-15</td>
<td>Stress-inducible TGF-β-related cytokine, weakly expressed under healthy conditions</td>
<td>Inflammation, aging, tissue injury</td>
</tr>
<tr>
<td>h-FABP</td>
<td>Widely expressed cytoplasmic protein enriched in striated muscles</td>
<td>Myocyte ischemia and injury</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>Hepatic acute phase protein induced during acute and chronic inflammation</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IL-6</td>
<td>Proinflammatory cytokine</td>
<td>Inflammation</td>
</tr>
<tr>
<td>IMA</td>
<td>Serum protein, N-terminus is modified upon tissue (cardiac) ischemia</td>
<td>Tissue ischemia</td>
</tr>
<tr>
<td>MPO</td>
<td>Inflammatory cell-derived secreted enzyme</td>
<td>Inflammation</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>Midregional fragment of proadrenomedullin, expressed by various tissues including the vasculature and the heart</td>
<td>Hemodynamic stress, inflammation</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>Midregional fragment of proatrial natriuretic peptide, produced mainly in the atria of the heart</td>
<td>Hemodynamic stress, volume overload</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Metalloproteinase secreted during inflammation and wound healing</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Soluble ST2</td>
<td>Soluble isoform of the IL-33 receptor, induced during T-cell activation, inflammation and fibrosis</td>
<td>Hemodynamic stress, inflammation</td>
</tr>
</tbody>
</table>

Table I Protein and peptide biomarkers in acute coronary syndrome.

Abbreviations: BNP, B-type natriuretic peptide; cTn, cardiac troponin; GDF-15, growth differentiation factor 15; h-FABP, heart-type fatty acid-binding protein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IMA, ischemia-modified albumin; MPO, myeloperoxidase; MR-proADM, midregional proadrenomedullin; MR-proANP, midregional proatrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAPP-A, pregnancy-associated plasma protein A; TGF, transforming growth factor.
somewhat lesser extent, N-terminal pro–B-type natriuretic peptide (NT-proBNP) emerged as the most promising biomarkers adding prognostic information to GRACE and high-sensitivity cTnT. Both biomarkers reclassified patients in the appropriate directions and across risk thresholds, which may trigger changes in treatment decisions in the future. Notably, addition of more than one biomarker added little discriminatory information, perhaps because the GRACE score already reflects several disease pathways, including heart failure (Killip class), renal function (creatinine concentration), ischemia (ECG), and myocyte injury (cTn). More widespread use of risk scores and prognostic biomarkers in clinical practice will help to identify high-risk patients who have the most to gain, in absolute terms, from established therapies.

There are some recent examples where biomarkers may help to select NSTE-ACS patients for specific therapies. In an exploratory analysis of the MERLIN–TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST elevation acute coronary syndromes—Thrombolysis In Myocardial Infarction 36) trial, ranolazine reduced the risk of cardiovascular death, MI, or recurrent ischemia only in patients with elevated B-type natriuretic peptide (BNP) levels, but not in those without. In the PLATO (PLAtelet inhibition and patient Outcomes) trial, elevated high-sensitivity cTnT levels predicted substantial benefit of ticagrelor over clopidogrel, whereas the benefits of ticagrelor were limited in those patients with normal high-sensitivity cTnT concentrations. Furthermore, the magnitude of benefit of ticagrelor was related to the degree of elevation of GDF-15 and NT-proBNP.

Recent studies have identified multiple biomarkers, including copeptin, GDF-15, midregional proadrenomedullin (MR-proADM), midregional proatrial natriuretic peptide (MR-proANP), and soluble ST2 that help identify patients at increased risk of heart failure after an episode of ACS, independent of clinical indicators and BNP. Remarkably, most of these biomarkers were only weakly or moderately correlated with each other, emphasizing that these markers are induced by distinct stressors, and suggesting that multiple mechanisms contribute to the development of heart failure after ACS. In the future, these biomarkers may help select patients for therapies aimed at mitigating the risk of heart failure after ACS.

The introduction of high-sensitivity cTn assays has resulted in an increased proportion of NSTE-ACS patients presenting with elevated cTn concentrations. Patients even with slight elevations of cTn (which could not be detected with previous less sensitive assays) are considered high risk and should undergo an early invasive strategy. As a result, current treatment recommendations for patients with NSTE-ACS have become more uniform, and less “personalized.” With a better understanding of the disease pathways reflected by circulating biomarkers, new treatment targets and a new taxonomy of ACS may emerge that will enable physicians to make more personalized and more effective treatment decisions.

Dr Wollert is named as coinventor on a patent for the use of GDF-15 for cardiovascular applications and has a contract with Roche Diagnostics for the development of a GDF-15 assay. Dr Wollert has received research grant funding from Roche Diagnostics.

REFERENCES

Using biomarkers to obtain mechanistic insight and guide management in ACS


Incorporating high-sensitivity cardiac troponin assays into clinical practice: these assays are your friend

Sara Love, PhD; Yader Sandoval, MD; Fred S. Apple, PhD

1Department of Laboratory Medicine and Pathology and 2Division of Cardiology, Department of Medicine, Hennepin County Medical Center, and University of Minnesota, Minneapolis, MN, USA

Correspondence: Dr Fred Apple, Hennepin County Medical Center, Clinical Laboratories P4, 701 Park Avenue, Minneapolis, MN 55415, USA
E-mail: apple004@umn.edu

Abstract
The objective of this review is to provide an overview of the current analytical, clinical, and risk assessment outcomes status of cardiac troponin (cTn) high-sensitivity (hs) assays and on how to better understand their use in clinical practice. The introduction of hs-cTnI and hs-cTnT assays into clinical practice has enabled improved diagnostic accuracy using serial changes. However, there remains substantial investigative work to be done before coherent evidence-based guidelines can be established for the full spectrum of available assays. Not all cTn assays, I or T, are alike, whether contemporary sensitive or high-sensitivity. Each assay and each platform on which cTn is measured requires development of its own evidence-based delta criteria in order to support optimal use for patients presenting with symptoms suggestive of ischemia. The growth in utilization of hs-cTn assays will both improve diagnostics for early rule in and early rule out of patients presenting with symptoms suggestive of acute coronary syndrome (ACS). As for patients with non-ACS presentation and for primary and or secondary prevention for risk assessment, future therapeutic studies will best define the power of hs-cTn assays and their role in clinical practice. However, what we do know is that an increased cTn concentration indicates a poor outcome and need for increased clinical vigilance.

Keywords: biomarkers; cardiac troponin; diagnostic accuracy; high-sensitivity assays; myocardial infarction; outcomes

Analytical performance
According to the 2012 Third Universal Definition of Myocardial Infarction, the preferred biomarker for detection of myocardial infarction (MI) is cardiac troponin (cTn). Any discussion of the clinical utility of cTn must begin with a brief discussion of the analytical
aspects of contemporary and hs-cTn assays, which are not standardized. This means that no two assays should be expected to provide equivalent concentration measurements from the same sample. This also means that laboratories should not interchange assays in clinical practice, as this will lead to clinical confusion. Readers interested in a more in-depth description of cTn biochemistry are directed to a detailed review by the International Federation of Clinical Chemistry (IFCC) Task Force on Clinical Applications of Cardiac Biomarkers. Based on the biochemistry of cTn, there is considerable complexity regarding standardization of cTn assays, arising from the many forms of circulating cTn in blood released from injured myocardial tissue, the heterogeneity of antibodies used in assays to detect different circulating cTn epitopes (Table I), as well as the lack of an acceptable primary reference material to uniformly calibrate all assays. Current recommendations endorse the use of two criteria for assay precision that earn the designation of “high sensitivity”: (i) a coefficient of variation (%CV) ≤10% at the 99th percentile upper reference limit (URL); and (ii) the ability to measure cTn in ≥50% LOD, µg/L | 99th Percentile, µg/L | 10% CV, µg/L | Epitopes recognized by capture (C) and detection (D) antibodies
---|---|---|---
Abbott AxSYM ADV | 0.02 | 0.04 | 0.16 | C: 87-91, 41-49; D: 24-40
Abbott ARCHITECT | 0.009 | 0.028 | 0.032 | C: 87-91, 24-40; D: 41-49
Abbott i-STAT | 0.02 | 0.08 | 0.10 | C: 41-49, 88-91; D: 28-39, 62-78
Alere Triage | 0.05 | <0.05 | NA | C: NA; D: 27-40
Alere Triage Cardio3* | 0.01 | 0.02 | NA | C: 27-39; D 83-93, 190-196
Beckman Access AccuTnI | 0.01 | 0.04 | 0.06 | C: 41-49; D: 24-40
bioMerieux Vidas Ultra | 0.01 | 0.01 | NA | NA
Mitsubishi Pathfast | 0.008 | 0.029 | NA | C: 41-49; D: 71-116, 163-209
Ortho Vitros ECi ES | 0.012 | 0.034 | 0.034 | C: 24-40, 41-49; D: 87-91
Radiometer AQ700 cTnI | 0.009 | 0.023 | 0.039 | C: 41-49, 190-196; D: 137-149
Radiometer AQ700 cTnT | 0.01 | <0.01 | 0.03 | C: 125-131; D: 136-147
Response RAMP | 0.03 | <0.01 | 0.21 | C: 85-92; D: 26-38
Roche E170/Elecsys 2010 | 0.01 | <0.01 | 0.03 | C: 125-131; D: 136-147
Siemens Centaur Ultra | 0.006 | 0.04 | 0.03 | C: 41-49, 87-91; D: 27-40
Siemens Dimension RxL | 0.04 | 0.07 | 0.14 | C: 27-32; D: 41-56
Siemens Immulite 2500 | 0.1 | 0.2 | 0.42 | C: 87-91; D: 27-40
Siemens Stratus CS | 0.03 | 0.07 | 0.06 | C: 27-32; D: 41-56
Siemens VISTA | 0.015 | 0.045 | 0.04 | C: 27-32; D: 41-56
Tosoh AIA II | 0.06 | <0.06 | 0.09 | C: 41-49; D: 87-91
Trinity Meritas | 0.012 | 0.019 | 0.024 | C: 24-40, 88-90; D: 137-147, 190-196
hs-cTnI* | | | | C: 125-131; D: 136-147
hs-cTnT* | | | | C: 125-131; D: 136-147

Table I Analytical characteristics of contemporary sensitive, point-of-care, and high-sensitivity cardiac troponin assays. *Available for use outside the USA as it is not cleared by the Food and Drug Administration; †In parentheses, the % of coefficient of variation at the 99th percentile upper reference limit.

Abbreviations: CV, coefficient of variation; hs-cTn, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; LOD, limit of detection; MTP, microtiter plate assay; NA, not available.


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of healthy reference subjects above an assay’s limit of detection (LOD). This allows high-sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT) assays to measure biological variation within a healthy population, allowing reference change values to be calculated (approximately 50%), and providing the ability to distinguish real cTn changes from analytical noise within the reference range.

Reviewing the literature will uncover substantial discrepancies in assay analytical features between claimed assay performance in manufacturers’ package inserts and peer-reviewed findings (Table I). One example of the heterogeneous nature of cTn assays comes from a reference range study from Apple. They found distinctively different 99th percentile URLs for the majority of 19 contemporary, point of care, and high-sensitivity cTnI and cTnT assays while examining a common set of reference samples, even for multiple assays from the same manufacturer. Furthermore, gender and age influence the distribution of troponin concentrations for both the hs-cTnI and hs-cTnT assays.

As a biomarker of myocardial injury, with irreversible myocyte damage releasing cTn, increased cTn levels do not indicate the etiology of damage, which makes clinical context key to their use and interpretation. The lack of diagnostic specificity becomes more complicated with the use of cTn measurements in clinical evaluations that are not related to acute coronary syndrome (ACS). Current guidelines for the diagnosis of ACS recommend serial measurement of cTn, including the use of hs-cTnI assays. Serial cTnI measurements (Figure 1) at presentation and over the following 2 to 3 hours for high-specificity assays or 6 hours for contemporary assays determines whether a rising or falling pattern above the URL is present, which distinguishes acute from chronic sources of myocardial necrosis or structural disease. Split sample replicates, run on both contemporary and hs-cTnI assays, have shown that hs-cTnI assays lead to fewer single cTn concentrations above the URL by virtue of the decreased analytical noise of these assays. Few false positive cTn values are observed with hs-cTnI assays. However, hemolysis may falsely increase cTn measured with hs-cTnI assays.

To better understand the implications of each hs-cTnI assay used in routine clinical practice, the following general points will assist clinicians. First, cTn results are not interchangeable, even for assays from a single manufacturer. Second, know what the 99th percentile URL is for the hs-cTn assay in use in your practice. At present, there is one hs-cTnI assay (Abbott Diagnostics) and one hs-cTnT assay (Roche Diagnostics) in clinical practice that meet the criteria outlined above. Third, follow at least 2 serial measurements over time. Look for an increasing or falling pattern, with at least one value above the 99th percentile URL to determine myocardial injury. Fourth, as high-sensitivity assays detect a larger number of non-ACS pathologies with concomitant myocardial injury, a single cTn value measured by a high-sensitivity assay will have a clinical specificity for MI as low as 65% to 75%. These are truly positive results, just not an indicator of MI. A delta value, the absolute concentration difference between two serial hs-cTn values, will assist in improving diagnostic specificity for MI to >90% with high-sensitivity assays. Fifth, hs-cTnI assays have concentration units expressed in whole numbers, ie, 10 ng/L, compared with contemporary assays that use μg/L, ie, 0.010 μg/L.

Clinical diagnostics

Reaching a diagnosis of acute MI is facilitated by the use of cTnI assays with optimal precision that are able to reliably detect changing values over time. Herein lies the clinical value of hs-cTnI assays, which are characterized by guideline-acceptable precision. hs-cTnI assays are appealing due to their ability to rule in or rule out acute MI more rapidly, shifting testing from a 6-hour window for contemporary assays to a 2- to 3-hour window for high-sensitivity assays. Figure 1 displays the serial concentration differences found between contemporary and hs-cTnI assays during the early course of an acute MI. Using a hs-
cTnI assay, Keller demonstrated in a European study that by combining the 99th percentile URL at admission with the serial change in hs-cTn concentrations within 3 hours, the positive predictive value (rule in MI) increased from 75.1% at admission to 95.8% after 3 hours. By applying the 99th percentile to a second hs-cTn measurement, ruling out MI at 3 hours was shown to have a negative predictive value of 99.4%. Similarly using the hs-cTnT assay, Reichlin demonstrated the clinical utility of absolute and relative hs-cTnT changes in the early diagnosis of acute MI. They showed that the sensitivity obtained by absolute changes in hs-cTnT according to baseline levels (≥14 ng/L) at 2 hours was 90%, whereas the positive and negative predictive value were 76% (at 0 h [baseline]) and 95% (at 2 h) respectively.

The role of hs-cTn assays in reducing unnecessary hospital admissions and potentially reducing costs by excluding acute MI has been studied (utilizing values below the 99th percentile). Using a cutoff of 3 ng/L limit of blank for a hs-cTnT assay, Body et al demonstrated a sensitivity and negative predictive value of 100%, including those with a symptom onset of less than 3 hours. Bandstein further reported a negative predictive value for MI within 30 days of 99.8% among patients with hs-cTnT assay values <5 ng/L (LOD) and nonspecific electrocardiograms.

From a diagnostic perspective, the conceivable advantages of using hs-cTn assays over contemporary cTn assays rely primarily on the possibility of improving our ability to rule in MI sooner; improved analytical precision at lower cTn concentrations allows clinicians to reliably follow serial concentration changes over time. Figure 2 demonstrates how the improved precision at the 99th percentile using a hs-cTn assay can decrease false positive MI diagnoses that occur with the use of the less precise contemporary cTn assays. Cullen, using a protocol combining the TIMI (Thrombolysis In Myocardial Infarction) risk score, electrocardiography, and 0- and 2-hour hs-cTn measurements, has also demonstrated the potential to decrease observation periods and admissions for approximately 40% of patients with suspected ACS.

However, there are several challenges that clinicians may encounter with the implementation of hs-cTn assays. First, hs-cTnT assays identify a higher number of results above the 99th percentile URL. Reichlin compared contemporary and hs-cTnT assays at presentation and demonstrated 22% versus 36% had increased concentrations above the 99th percentiles, respectively. Second, using the hs-cTnT assay resulted in an increased incidence of acute MI (from 198 with contemporary assay to 242 with hs-cTnT assay); due to 44 additional non-ST elevation MIs (35 type 1 MIs, 9 type 2 MIs). These findings coincided with a decrease in the incidence of unstable angina; from 151 to 122 cases, respectively. Third, the higher frequency of cTn increases encountered using hs-cTn assays identifies a larger subset of patients having myocardial injury. Myocardial injury may be: (i) primary myocardial ischemia (eg, plaque rupture); (ii) a supply/demand imbalance of myocardial ischemia (eg, arrhythmia); (iii) unrelated to myocardial ischemia (eg, cardiac contusion, myocarditis, etc); or (iv) linked to multifactorial/indeterminate causes (eg, renal failure, sepsis in critically ill patients, heart failure, etc). Consequently, clinicians will be frequently faced with the challenge of deciding whether increased values are due to acute or chronic conditions, and if acute, whether increases are due to type 1 MI, type 2 MI, or an alternate non-MI condition that has increased hs-cTn (Table II). Discerning these conditions is a challenge in itself and is of major importance due to the distinct therapeutic approaches required, particularly in type 1 MI.

Fourth, the challenge of how to assess and incorporate serial hs-cTn changes, or deltas, into clinical practice will be important to differentiate acute from chronic/static myocardial injury. Gaps exist as to how studies should be carried out to define delta changes to diagnose or exclude acute MI. Deltas will need to be individualized by hs-cTn assay because of their

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**Fig. 2** Improved precision of a high-sensitivity cardiac troponin I (hs-cTnI) assay decreases false positive diagnoses of myocardial infarction compared with a less precise contemporary cardiac troponin I (cTnI) assay.


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**Table II**

<table>
<thead>
<tr>
<th>hs-cTnI Cutoff</th>
<th>Male hs-cTnI cutoff</th>
<th>Female hs-cTnI cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 ng/L</td>
<td>16 ng/L</td>
<td></td>
</tr>
<tr>
<td>30 ng/L</td>
<td>26 ng/L</td>
<td></td>
</tr>
<tr>
<td>26 ng/L</td>
<td>19 ng/L</td>
<td></td>
</tr>
<tr>
<td>34 ng/L</td>
<td>16 ng/L</td>
<td></td>
</tr>
<tr>
<td>26 ng/L</td>
<td>19 ng/L</td>
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</tr>
</tbody>
</table>

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unique analytical and biological characteristics due to the lack of assay standardization. Early evidence points toward establishing an absolute concentration delta over a 2-hour period after presentation. It is important to acknowledge that each individual cTn assay will require a specific delta determination for both absolute and percent delta changes. A convenient approach to the delta value, such as the 20% relative change proposed by the National Academy of Clinical Collaboration (NACB) laboratory medicine practice guidelines in 2007, should be abandoned, as it does not perform as well as a delta optimized for the individual assay.\textsuperscript{24} The primary aim of using a delta criterion has been to provide improved clinical specificity compared with a single determination using the 99th percentile URL, not to improve sensitivity.

**Risk stratification and outcomes assessment**

Both hs-cTnI and hs-cTnT assays have been shown to: (i) risk-stratify symptomatic and stable ACS patients in both the short term (admission) and the long term (over 6 months), for major adverse cardiac events; (ii) identify nonischemic (non-ACS) pathologies that cause myocardial injury (Table II) and demonstrate that patients with them are at higher risk of adverse outcomes compared with ACS patients; and (iii) predict cardiovascular mortality in the ambulatory community or multiethnic populations with or without known coronary artery disease, in whom increased hs-cTn values are associated with structural heart disease and chronic kidney disease.\textsuperscript{25-30} What distinguishes hs-cTn assays from contemporary assays is their ability to precisely measure very low cTnI and cTnT concentrations (1-20 ng/L), which is below the LOD of contemporary assays used in clinical practice today.\textsuperscript{2} This added analytical sensitivity allows hs-cTn assays to reliably measure concentrations in almost 100% of healthy individuals, compared with contemporary assays that measure values in only <20% of healthy individuals. Future studies will be necessary to define the role of hs-cTn assays in screening apparently healthy individuals to estimate their risk of future events, and how potential interventions may influence their outcomes.

**Conclusion**

The introduction of hs-cTnI and hs-cTnT assays into clinical practice has enabled improved diagnostic accuracy using serial changes. However, there remains substantial investigative work to be done before coherent evidence-based guidelines can be established for the full spectrum of available assays.\textsuperscript{31} Not all cTn assays, T or I, are alike, whether conventional or high-sensitivity. Each assay and each platform on which cTn is measured requires development of its own evidence-based delta criteria in order to support optimal use for patients presenting with symptoms suggestive of ischemia.\textsuperscript{1,32} The growth in utilization of hs-cTn assays will improve diagnostics for early rule in and early rule out of patients presenting with symptoms suggestive of ACS. As for patients with non-ACS presentation and for primary and/or secondary prevention for risk assessment, future therapeutic studies will best define the power of hs-cTn assays and their role in clinical practice. However, what we do know is that an increased cTn concentration points toward a poor outcome and need for appropriate management.

### Table II

**Pathological etiologies that cause cardiac troponin to increase above the 99th percentile upper reference limit.**

<table>
<thead>
<tr>
<th>Pathological etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury related to primary myocardial ischemia</td>
</tr>
<tr>
<td>Atherosclerotic plaque rupture</td>
</tr>
<tr>
<td>Intraluminal coronary artery thrombus formation</td>
</tr>
<tr>
<td>Injury related to supply/demand imbalance of myocardial ischemia</td>
</tr>
<tr>
<td>Tachy- or bradyarrhythmias</td>
</tr>
<tr>
<td>Aortic dissection or severe aortic valve disease</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Cardiogenic, hypovolemic, or septic shock</td>
</tr>
<tr>
<td>Severe respiratory failure</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
<tr>
<td>Hypertension with or without LVH</td>
</tr>
<tr>
<td>Coronary spasm</td>
</tr>
<tr>
<td>Coronary embolism or vasculitis</td>
</tr>
<tr>
<td>Coronary endothelial dysfunction without significant CAD</td>
</tr>
<tr>
<td>Injury not related to myocardial ischemia</td>
</tr>
<tr>
<td>Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks</td>
</tr>
<tr>
<td>Rhabdomyolysis with cardiac involvement</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td>Cardiotoxic agents, eg, anthracyclines, herceptin</td>
</tr>
<tr>
<td>Multifactorial or indeterminate myocardial injury</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Stress (takotsubo) cardiomyopathy</td>
</tr>
<tr>
<td>Severe pulmonary embolism or pulmonary hypertension</td>
</tr>
<tr>
<td>Septis and critically ill patients</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Severe acute neurological diseases, eg, stroke, subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Infiltrative diseases, eg, amyloidosis, sarcoidosis</td>
</tr>
<tr>
<td>Strenuous exercise</td>
</tr>
</tbody>
</table>


**Abbreviations:** CAD, coronary artery disease; LVH, left ventricular hypertrophy.
REFERENCES


Myocardial infarction (MI) with nonobstructed (<50% stenosis) coronary arteries (MINOCA) occurs in approximately 6% of patients with suspected MI and represents a diagnostic and therapeutic dilemma.1 The prevalence may be even higher in the era of high-sensitivity cardiac troponin (cTn) assays, because of their lower specificity to diagnose acute MI. It typically occurs in younger patients and an unsatisfying number of patients are ultimately discharged without a clear etiology for their episode of myocardial injury. Importantly, patients have an adverse outcome that may be related to inappropriate diagnosis and treatment.2

The underlying causes of MINOCA are heterogeneous and include plaque rupture with spontaneous coronary recanalization and/or distal embolization of plaque debris, coronary spasm, myocarditis, stress cardiomyopathy, pulmonary embolism, microvascular dysfunction, and others (Table I). Given this wide spectrum of potential diagnoses, it follows that the pathology is not exclusively related to MI, but includes non-MI diagnoses as well.

A crucial question is whether MINOCA is associated with vulnerable plaques or not. In more than half of patients with MINOCA, some degree of coronary artery disease (CAD) can be found, including outward/positively remodeled atherosclerotic plaque within a coronary artery.3 Although MI is frequently triggered by atherosclerotic plaques which previously did not cause severe stenosis,4 holding such plaques responsible for the index event in patients with MINOCA is jumping to conclusions. This “smoking gun” theory is also challenged by the observation that an equal burden of CAD can be found in matched healthy controls without known cardiovascular disease5 and that MI is finally diagnosed in only 20% of patients.1
The presence of minimal CAD can merely be a coincidental finding. Alternatively, microvascular disease as a result of coronary vasomotor dysfunction and/or decreased intramyocardial capillary density in hypertensive or diabetic patients or in hypertrophic cardiomyopathy, are increasingly recognized entities. 

Other non-MI diagnoses should be taken into account and inappropriate treatment and stigmatization of patients, as having suffered a MI, should be avoided. Current guidelines do not provide recommendations on how to deal with these patients, but additional diagnostic testing is often needed to narrow the differential diagnosis.

### Initial diagnostic evaluation

The interventional cardiologist is often the first to be confronted with MINOCA. Myocardial bridging, spontaneous coronary dissection, and missed proximally occluded side-branches should carefully be excluded. Provocative testing using intracoronary ergonovine or acetylcholine can be performed to exclude coronary vasospasm as a result of endothelial dysfunction and concealed atherosclerosis. Because coronary angiography does not allow visualization of the vessel wall, vulnerable plaques could be sought using either intravascular ultrasound (IVUS) or optical coherence tomography (OCT) while the patient is still in the catheterization lab. A thin fibrous cap, large plaque burden, large lipid core, and small lumen area are morphological characteristics of ruptured and vulnerable coronary plaques. However, an extensive and “blind” exploration of the complete coronary tree in search for concealed atherosclerosis is impractical, time-consuming and not without risk. Restricted availability, expertise, higher costs, and additional radiation exposure for patients further limit widespread use of OCT and IVUS. Moreover, far too many patients are sent back to the ward without further invasive testing, leaving the clinician in despair.

Clinical characteristics are not specific, but can be useful to narrow the differential diagnosis. The presence of multiple risk factors for atherosclerosis (smoking, abnormal lipid profile, positive family history, diabetes, hypertension) increases the likelihood of concealed atherosclerosis. A family or personal history of hypercoagulability and thromboembolism may warrant a search for hereditary thrombophilia, such as factor V Leiden, prothrombin G20210A gene mutation, protein C, protein S, antithrombin deficiency, hyperhomocysteinemia, or the antiphospholipid antibody syndrome. Routine blood testing may reveal elevated inflammatory parameters or elevated D-dimer levels that may suggest myocarditis or pulmonary embolism, respectively. However, the information received from history or additional blood tests often lacks specificity and provides evidence too circumstantial to be clinically useful. Additional noninvasive imaging may further narrow the differential diagnosis.

### Abbreviations

- CAD: coronary artery disease; CT: computed tomography; cTn: cardiac troponin; IVUS: intravascular ultrasound; MINOCA: myocardial infarction with nonobstructed coronary arteries; MRI: magnetic resonance imaging; OCT: optical coherence tomography; WMA: wall motion abnormality

### Table I

<table>
<thead>
<tr>
<th>MI related</th>
<th>Non-MI related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque rupture or erosion and spontaneous recanalization</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Coronary spasm in setting of - Endothelial dysfunction - Cocaine abuse - Ephedrine-containing drug abuse - Withdrawal from calcium antagonists</td>
<td>Stress cardiomyopathy Pulmonary embolism Dilated cardiomyopathy Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>(Paradoxical) coronary embolism - Myocardial tumor (myxoma) - Myocardial thrombus (post-MI, atrial fibrillation) - PFO or ASD</td>
<td>Microvascular dysfunction (syndrome X) Phaeochromocytoma Sarcoïdosis Connective tissue disease (SLE)</td>
</tr>
<tr>
<td>Hypercoagulable status - Factor V Leiden - Prothrombin G20210A gene mutation - Protein C deficiency - Protein S deficiency - Antithrombin deficiency - Hyperhomocysteinemia - Antiphospholipid antibody syndrome</td>
<td></td>
</tr>
<tr>
<td>Myocardial bridging</td>
<td></td>
</tr>
<tr>
<td>Demand ischemia - Tachycardia (eg, atrial fibrillation) - Severe hypertension (&gt;200 mm Hg systolic) - Congestive heart failure</td>
<td></td>
</tr>
</tbody>
</table>

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Table I: Potential causes of myocardial infarction with nonobstructed coronary arteries (MINOCA).

Abbreviations: ASD, atrial septal defect; MI, myocardial infarction; PFO, patent foramen ovale; SLE, systemic lupus erythematosus.
Noninvasive imaging

Cardiac magnetic resonance imaging

Although a single test that untangles all different etiologies in patients with MINOCA is not available, cardiac magnetic resonance imaging (MRI) may differentiate between potential causes. A comprehensive cardiac MRI examination provides information on myocardial function (cine imaging), inflammation (T2-weighted imaging), and fibrosis (delayed enhancement imaging), and allows categorization of potential etiologies, both MI- and non-MI–related.10

Cardiac cine MRI accurately and reproducibly provides assessment of cardiac function, volumes, mass, and morphology. Consequently, regional wall motion abnormalities (WMAs) that are confined to a corresponding coronary artery territory are highly suspicious, but not diagnostic for MI. WMAs outside a single coronary artery territory or extending over multiple territories occur with either myocarditis or stress cardiomyopathy. Dilated or hypertrophic cardiomyopathy can also be suggested from cardiac cine MRI.

T2-weighted cardiac MRI enables visualization of myocardial edema (T2-hyperintensity) and may be used to detect acute MI, myocarditis, or stress cardiomyopathy.11 In acute MI, edema is typically subendocardial or transmural, and sometimes accompanied with intramyocardial hemorrhage (central hypoenhancement within hyperenhanced area) (Figure 1, case 1). In myocarditis, T2-hyperintensity is mostly patchy, mid-wall, or epicardial, and located in the septal and/or basal inferolateral segments (Figure 1, case 2). A cardinal feature of stress cardiomyopathy (also “takotsubo cardiomyopathy” or “transient apical ballooning”) is reversible regional WMAs and edema that extends beyond a single...
coronary artery in the absence of myocardial scar and is often triggered by emotional or physical stress.11

Delayed enhancement cardiac MRI is capable of visualizing small scars that cannot be detected by other imaging techniques and allows differentiation between MI- and non-MI–related etiologies.10 Based on the concept that ischemic necrosis proceeds as a “wavefront” from the subendocardium to the epicardium with increasing occlusion time, it follows that hyperenhancement patterns that spare the subendocardium are likely to be nonischemic in origin. Thus, ischemic damage from CAD typically involves the endocardium,10 whereas mid-wall to epicardial scar (either patchy or linear) is consistent with myocarditis or dilated or hypertrophic cardiomyopathy. In such cases, the coronary angiogram should be reassessed for proximally occluded side branches that may have been missed initially.

A specific diagnosis can be provided by cardiac MRI in up to 75% of patients with MINOCA12 and include MI (5% to 29%), myocarditis (7% to 63%), stress cardiomyopathy (2% to 22%), pericarditis (0% to 5%), amyloidosis (0% to 5%), and hypertrophic or dilated cardiomyopathy (0% to 4%).13 Nonetheless, a large subset of patients do not have any abnormalities on cardiac MRI.1 This may be explained by an insufficient resolution of cardiac MRI to detect limited myocardial damage, disease recovery (eg, stress cardiomyopathy [for this reason cardiac MRI should be performed early]), or other etiologies for MINOCA undetectable by cardiac MRI. New developments, such as T1- and T2-mapping techniques may further increase cardiac MRI’s diagnostic accuracy, but validation is still awaited.14 The diagnostic role of adenosine stress-perfusion cardiac MRI to detect microvascular disease is still debated.

**Fig. 2** Potential diagnostic strategy in patients with MINOCA. *When available. †Perform "triple rule out" CT when high suspicion for pulmonary embolism or acute aortic dissection (elevated D-dimer).

**Abbreviations:** ACS, acute coronary syndrome; ASD, atrial septal defect; CAD, coronary artery disease; CMP, cardiomyopathy; CMR, cardiac magnetic resonance imaging; CT, computed tomography; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IVUS, intravascular ultrasound; LV, left ventricle; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructed coronary arteries; OCT, optical coherence tomography; PFO, patent foramen ovale; WMA, wall motion abnormalities.
Computed tomography angiography

Atherosclerosis may be present, but concealed on routine invasive coronary angiography because of outward remodeling of atherosclerotic plaques. Computed tomography (CT) angiography is very sensitive in detecting CAD and rules out atherosclerosis with high confidence. Initial noncontrast enhanced CT scanning may identify calcified coronary plaques, but when absent, does not rule out the existence of noncalcified plaques. Therefore, iodine contrast agents are usually administered to visualize the coronary lumen, the vascular wall, and (noncalcified) plaques. Completely normal coronary arteries on CT angiography and a zero calcium score exclude atherosclerotic CAD as a cause for MINOCA.

In the presence of atherosclerosis, CT angiography allows characterization of plaques. In general, vulnerable plaques are noncalcified, have a large plaque area, a large lipid core, and more frequently show outward remodeling. The high resolution of CT angiography allows identification of ruptured plaques, but is insufficient to detect the thinned fibrous cap of eroded plaques. Even though there are no distinct characteristics for plaque erosion, the presence of a ruptured or vulnerable plaque may be sufficient to indicate a plaque-related etiology in a patient with MINOCA.

In addition to coronary artery evaluation, specific contrast bolus protocols allow opacification of coronary arteries, the aorta, and the pulmonary arteries in a single CT angiography scan (“triple rule out” protocol). Using this comprehensive scanning protocol may be beneficial in selected patients to quickly rule out CAD, aortic dissection, and pulmonary embolism (Figure 1, case 3). Furthermore, CT may identify other clinically important diagnoses such as a coronary anomaly, malignancy, or pneumonia.

Conclusion

Diagnosing patients with MINOCA remains challenging and includes both MI- and non-MI–related diagnoses. The diagnostic algorithm should start in the catheterization lab, followed by a staged use of noninvasive imaging techniques (Figure 2). Cardiac MRI plays a crucial role in narrowing the differential diagnosis. In combination with results from the history, and invasive (OCT or IVUS) or noninvasive techniques (CT), CAD is ruled out or becomes more plausible. In the setting of MI without CAD, a thorough search should be performed for (paradoxical) coronary embolism (exclude atrial fibrillation, myocardial tumor or thrombus, patent foramen ovale, or atrial septal defect) or hypercoagulability disorders. Unfortunately, in an unsatisfying number of patients, the etiology remains unknown.

REFERENCES

Metabolites are the intermediate and end products of all metabolic processes; a change in metabolic profiles is therefore an integrated read-out of cellular processes in health and disease. Complementary to other “omic” technologies, metabolomics, including the subbranch of lipidomics, aims to capture the vast range of small molecules involved in metabolomic networks. Technological advances in high-resolution mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR) have been at the forefront of metabolic research. NMR is widely used, especially for metabolic profiling of large clinical cohorts, owing to high throughput and relatively low costs, but MS has become the analytical platform of choice for metabolite profiling. MS can be performed in a targeted and untargeted manner. Untargeted analysis of metabolites has the potential to reveal previously unknown pathophysiological mechanisms by the simultaneous assessment of multiple metabolic pathways. Targeted analysis, on the other hand, can be used to quantify specific metabolites with greater specificity and sensitivity, with the possibility of determining absolute concentrations using authentic standards.

Cardiovascular diseases (CVDs) are intrinsically linked with metabolic disorders, namely obesity, dyslipidemia, insulin resistance, and type 2 diabetes mellitus (T2DM). Thus, the technical advances for metabolic
profiling will be particularly useful for studying cardiometabolic disorders. Insulin resistance, for example, can exist for years without manifestation of clinical symptoms of T2DM and early detection of insulin resistance may allow effective interventions in order to delay onset and prevent complications like CVD. Here we review key findings of metabolomics studies looking at cardiometabolic diseases (Figure 1).

**Metabolic disorders**  
Insulin resistance, diabetes, obesity, dyslipidemia  
Associated with changes in

- Amino acids
- Diet-related ammonium compounds
- Nucleotides
- Lipids

**Cardiovascular diseases**  
Atherosclerosis, myocardial infarction, ischemia, heart failure

Monitoring levels may give an early indication of

**Fig. 1 Metabolomics and cardiovascular disease (CVD). Overview of metabolites with reported associations to CVD.**

**Abbreviations:** BB, butyrobetaine; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

**Branched-chain amino acids and type 2 diabetes mellitus**

Increased levels of branched-chain amino acids (BCAAs) contribute to insulin resistance and predict T2DM. In a cross-sectional study, Newgard et al documented differences in blood metabolite profiles of 74 obese and 67 lean individuals, with significant differences found in the abundance of BCAAs (valine, leucine, and isoleucine) as well as acylcarnitines (C3 and C5) and other amino acids. Obese subjects displayed a BCAA “signature” by which dysregulated BCAA metabolism (due to overload) contributes to the development of insulin resistance and glucose intolerance, leading to T2DM. In rats, dietary BCAAs seemed to induce mammalian target of rapamycin (mTOR)–insulin receptor substrate-1 phosphorylation and treatment with rapamycin, an mTOR inhibitor, alleviated insulin resistance only in rats fed a BCAA/high-fat diet compared with rats fed a high-fat diet only. Expanding on these findings by the Newgard group, Wang et al confirmed BCAAs as potential biomarkers for incident T2DM in two large, longitudinal studies. The results showed baseline levels of five branched-chain and aromatic amino acids (isoleucine, leucine, valine, tyrosine, and phenylalanine) to be significantly associated with future T2DM, highlighting the potential of monitoring amino acid metabolism in addition to established markers of glucose metabolism to detect early manifestations of T2DM.

**Acylcarnitines and coronary artery disease**

Shah et al used targeted liquid chromatography–MS/MS and isotopically labeled standards for absolute quantitation of 69 metabolites in coronary artery disease (CAD) patients (who underwent cardiac catheterization) and controls from the CATHeterization GENetics (CATHGEN) biorepository. As well as changes in glutamate/glutamine, proline, methionine, and urea cycle metabolites, the BCAAs leucine, isoleucine, and valine were also associated with CAD. As expected, T2DM was more prevalent among cases than controls. After statistical adjustment for T2DM, however, a significant association of circulating BCAAs with CAD remained, indicating that changes in BCAAs may either identify patients with insulin resistance before manifestation of T2DM or that in addition, the BCAA pathway is also associated with CAD. A further signature composed of short-chain dicarboxylylcarnitines was not only associated with the prevalence of CAD, but also with occurrence of death or myocardial infarction (MI) during a median of almost 3 years of follow-up in patients with existing CAD. Carnitine, with its predominant source in red meat, is required for the import of long-chain fatty acids into mitochon-
Choline/trimethylamine N-oxide and cardiovascular risk

Another known diet-related metabolite is choline. In a study by Wang et al, metabolism of dietary phosphatidylcholine by the gut flora was shown to increase risk of atherosclerosis and CVD by generating the catabolites choline, trimethylamine N-oxide (TMAO), and betaine in both humans and mice. Dietary choline promoted the formation of atherosclerotic plaques in mice, and this could be prevented by antibiotic treatment. A distinct second pathway for TMAO formation was highlighted by Koeth et al: supplementation of \( \gamma \)-butyrobetaine, a gut microbial intermediate in the metabolism of L-carnitine to trimethylamine and TMAO, also increases atherosclerotic plaque area significantly (50%) in mice. Again, no increase was observed in \( \gamma \)-butyrobetaine–fed mice when given an antibiotic cocktail to suppress gut microbes. More recent findings, however, would suggest that the association between TMAO and CVD could, at least partially, be explained by impaired kidney dysfunction. TMAO levels are greatly influenced by the glomerular filtration rate and are elevated in chronic kidney diseases. Renal impairment is a well-established cardiovascular risk factor, putting into question the causal relationship of dietary choline and CVD. Similarly, impaired renal clearance could contribute to increased systemic TMAO levels in patients with stable heart failure; elevated TMAO was associated with more than a 3-fold increase in mortality.

Metabolomics in myocardial ischemia and infarction

Ischemia leads to impaired adenosine triphosphate (ATP) metabolism and causes an accumulation of sequential purine degradation products [adenosine diphosphate (ADP), adenosine monophosphate (AMP), inosine, hypoxanthine, and xanthine]. Using targeted MS metabolomics and plasma samples from 36 patients before and after exercise testing, Sabatine et al reported elevated lactic acid and metabolites involved in skeletal muscle AMP catabolism as well as significant changes in six members of the citric acid pathway in response to myocardial ischemia after exercise. Lactate and glucose have also been found to predict exercise-induced ischemia in patients with suspected CAD in blood samples obtained before exercise. In patients undergoing alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy, Lewis et al analyzed serial blood samples from the coronary sinus and periphery. Metabolite profiles by targeted MS were compared to identify markers associated with induced MI. Changes in metabolites were detected as early as 10 minutes after planned MI producing a metabolic signature consisting of aconitic acid, TMAO, threonine, and hypoxanthine, all of which differentiated patients with spontaneous MI from those undergoing diagnostic coronary angiography. Purine degradation products, namely hypoxanthine and xanthine, have been proposed to be potentially useful markers of ischemia. They not only increase in the circulation after induced MI, but the urinary excretion of hypoxanthine and xanthine is also elevated in acute coronary syndrome (ACS) patients. A point to note is that alterations in these metabolites were seen when no significant rises in the clinically available biomarkers, myocardial creatine kinase (CK-MB) and troponin T, were detectable in the plasma, illustrating the potential of metabolites to detect the presence of very early myocardial injury; no currently used biomarkers are elevated within a time frame of 10 minutes. A caveat of using metabolites as biomarkers for cardiac ischemia is the lack of tissue specificity. Unlike cardiac troponins, these metabolites are ubiquitously present.

Another study by Vallejo et al used a gas chromatography–MS platform to compare the “metabolomic fingerprint” of plasma samples from patients with non–ST-segment elevation ACS, stable atherosclerosis, and healthy patients (n=9-10 per group). Among other changes, 4-hydroxyproline was found to decrease in ACS patients compared with controls. Change in 4-hydroxyproline is of interest as it is a component of collagens. The vascular extracellular matrix stabilizes atherosclerotic plaques to help...
prevent rupture. Circulating levels of 4-hydroxyproline are also thought to prevent the binding of low-density lipoprotein (LDL) to lipoproteins previously deposited in the vascular wall and to release already deposited LDL from atherosclerotic lesions.15

**Lipidomics and cardiovascular risk**

Traditionally, cardiovascular research focused mainly on the role of lipid classes rather than individual molecular species. Recent studies, however, highlight the importance of recognizing subtypes of lipids. Detailed knowledge of how individual lipid species contribute to pathophysiology of CVD may provide better biomarkers and novel therapeutic targets.16 We have performed MS-based lipidomics in the prospective, population-based Bruneck study to identify molecular lipid signatures for cardiovascular risk; triacylglycerols and cholesterol esters with low carbon number and double-bond content were associated with predicting CVD events over a 10-year period,17 including triacylglycerol 54:2 and cholesterol ester 16:1. The observed shift in fatty acid composition in complex lipids would be consistent with fatty acids derived from hepatic de novo lipogenesis (14:0 [myristic acid], 16:0 [palmitic acid], 18:0 [stearic acid], 16:1 [palmitoleic acid], and 18:1 [oleic acid]) being associated with a higher CVD risk than essential fatty acids. Subsets of triacylglycerols with the same nonessential fatty acids were also associated with increased risk of T2DM.18 In the EPIC (European Prospective Investigation into Cancer and nutrition)-InterAct case-cohort study, the even-chain saturated fatty acids (14:0, 16:0, and 18:0) were positively associated with incident T2DM.19 The ratio of 16:1 (n-7) to 16:0 was significantly positively associated with T2DM, but the ratio of 18:1 (n-9) to 18:0 was not. Unlike even-chain saturated fatty acids, odd-chain saturated fatty acids displayed an inverse relationship with the risk of T2DM, showing that not all saturated fatty acids have an adverse effect as conventionally classified.19

As expected, elevated levels of most lipid classes are associated with increased cardiovascular risk.17 Lysophosphatidylcholines (LPCs), however, showed an inverse relationship with incident CVD in the Bruneck study.17 A similar inverse association between LPCs and CVD were demonstrated by Ganna and colleagues investigating metabolic profiles of more than 3600 individuals from three population-based studies.20 Using both an untargeted and targeted MS approach, the authors identified four metabolites to be associated with incident coronary heart disease, independently of main cardiovascular risk factors; LPCs 18:1 and 18:2, monoglyceride 18:2, and sphingomyelin 28:1. LPCs were negatively associated with body mass index, markers of inflammation, and subclinical CVD, whereas the opposite was the case for monoglyceride 18:2. When added to a model for risk prediction, monoglyceride 18:2 was a better predictor of coronary heart disease compared with triacylglycerol levels. It was associated with higher levels of cardiovascular risk factors and markers of subclinical CVD and oxidative stress.20 Notably, LPC 18:2 has also been found to be inversely associated with incident T2DM and impaired glucose tolerance.21

**Conclusions and future outlook**

Both untargeted and targeted metabolomics will improve the identification of pathophysiological disturbances in metabolic networks. Enzymatic activities are the determinants of metabolite levels, thus to understand biological systems, small molecule metabolite data should be integrated with other “omics” analysis.1 Although targeted methods can provide absolute measurements with the use of labeled standards, this inevitably means that one is limited to changes in metabolites whose retention times and MS parameters have been incorporated into the MS method. Knowledge of the human metabolome is anticipated to grow, hence untargeted methods are useful for hypothesis-free discovery analysis. As the use of single metabolites may lack sensitivity or specificity for risk stratification,22 risk assessment can be improved by using multiple biomarkers to create a systems-level integration of “metabolomics” data.23 To aid in this complex analysis, the use of computational algorithms is a requirement. Further understanding of metabolic networks may advance our understanding of the underlying mechanisms of CVD, as well as improve risk prediction and aid the development of novel therapeutic interventions.
What can we learn from metabolomics?

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Trimetazidine effects on cardiac biomarkers in acute coronary syndrome

Dr Jamshed Jal Dalal, MD, PhD
Director of the Center for Cardiac Sciences, Kokilaben Dhirubhai Ambani Hospital, Mumbai, India

Correspondence: Dr Jamshed Jal Dalal, Director of the Center for Cardiac Sciences, Kokilaben Dhirubhai Ambani Hospital, Four Bungalows, Andheri West, Mumbai 400053, India
E-mail: jjdalal@hotmail.com

Abstract
Trimetazidine acts at the cellular level, increasing myocardial glucose oxidation and shifting substrate utilization from fatty acid to carbohydrate metabolism. In an ischemic situation, this promotes the formation of adenosine triphosphate, the main source of cardiac energy, at less oxygen cost. The benefit on myocyte necrosis can be judged by reduction in release of biomarkers such as cardiac troponin, myocardial creatine kinase, brain natriuretic peptide, and interleukin 6. These beneficial effects of trimetazidine have been recorded in patients with acute coronary syndrome, treated medically or by percutaneous intervention or coronary artery bypass graft surgery. What is most gratifying is that these effects on cellular protection are associated with clinical improvement in symptoms, left ventricular function, cardiac events, and even mortality. ■ Heart Metab. 2015;67:26-29

Keywords: acute coronary syndrome; cardiac biomarker; metabolic management; trimetazidine

Trimetazidine is a drug which treats myocardial ischemia through a metabolic pathway without having any hemodynamic effects. The metabolic effect is mediated by inhibition of mitochondrial long-chain 3-ketoacyl CoA thiolase, an enzyme that operates in the free fatty acid (FFA) β-oxidative chain. Its key function is increasing myocardial glucose oxidation and shifting from fatty acid to carbohydrate metabolism. This allows adenosine triphosphate (ATP) formation using less oxygen, which is deficient in ischemia. Although FFAs are a major source of ATP production in the heart, they require more oxygen than glucose to produce an equivalent amount of ATP. As a result, during ischemia, fatty acids are not as efficient a source of energy as glucose. Furthermore, during ischemia, the products of glycolysis such as lactate and protons accumulate and promote an increase in intracellular sodium and calcium, which in turn require more ATP to reestablish ionic homeostasis. By reducing cytosolic concentrations of FFAs and hydrogen ions, the cell membrane is protected from irreversible damage. Trimetazidine also reduces reactive oxygen species, improving myocardial integrity. The protection of cellular integrity translates into cell survival and improved cardiac efficiency.

Benefits of trimetazidine have been documented for stable angina, acute coronary syndromes (ACS), heart failure (HF), and in stent restenosis. It potenti-
Effects of trimetazidine on cardiac biomarkers

Cardiac biomarkers such as cardiac troponin (cTn), high-sensitivity (hs) troponin, myocardial creatine kinase (CK-MB), and brain natriuretic peptide (BNP) have been well established in the diagnosis, management, and prognosis of cardiac diseases. The release of these markers can be used as a guide to determine the benefits of medical or interventional therapy. This article presents the effects of trimetazidine on biomarker release and demonstrates how this can be used to judge the efficacy of metabolic management of ischemia.

Biomarkers post–myocardial infarction

Pudil et al studied a population (average age 56 years) with acute myocardial infarction (AMI), admitted within 6 hours of onset of symptoms and treated with streptokinase. The trimetazidine group showed lower plasma E-selectin levels, and a significant reduction of plasma C-reactive protein level (CRP).8

In another study, 100 diabetic patients with AMI were prospectively enrolled and randomized to receive trimetazidine (group A, 50 patients) or placebo (group B, 50 patients), starting before thrombolysis.9 After 24 hours, 45 patients (90%) in group A vs 10 patients (20%) in group B showed peaking of cTn and CK-MB levels (P<0.05), suggesting less myocardial damage. Both biomarker levels were significantly higher in the placebo group at different sampling times (Figure 1).9 Complete resolution of ST-segment elevation was recorded in 70% of patients in group A vs 36% in group B (P<0.05). Six months later, group A showed a higher left ventricular ejection fraction (LVEF) and fewer cardiac adverse events (P<0.05). They concluded that in patients with AMI receiving thrombolytic therapy, trimetazidine was associated with less myocardial damage, earlier successful reperfusion, improvement of LVEF, and fewer cardiac adverse events.

Biomarkers post–percutaneous coronary intervention

Percutaneous coronary intervention (PCI) provides an ideal opportunity to study the effects of trimetazidine prior to induction and relief of ischemia. In a study of patients with non–ST-segment elevation myocardial infarction (NSTEMI), Demirelli showed that trimetazidine treatment, commenced prior to PCI and continued after PCI, improved left ventricular end-diastolic volume and decreased BNP levels.10

Bonello et al, in a study of 582 patients, demonstrated that trimetazidine resulted in a significant reduction in the postprocedural cardiac troponin I (cTnI) levels and in the total amount of cTn released (Figure 2).11 He concluded that preprocedural administration of trimetazidine significantly reduces PCI-induced myocardial infarction.11

In a study by Lin et al, 475 patients with ACS undergoing PCI were treated with trimetazidine and atorvastatin, or atorvastatin alone. Twenty-four hours post-PCI, cTnI concentration and myeloperoxidase were lower in the trimetazidine group (P<0.05). Six months later, group A showed a higher left ventricular ejection fraction (LVEF) and fewer cardiac adverse events (P<0.05). They concluded that in patients with ACS receiving PCI, trimetazidine was associated with less myocardial damage, earlier successful reperfusion, improvement of LVEF, and fewer cardiac adverse events.
oxidase activity were significantly lower ($P<0.05$) in the trimetazidine group; however, CK-MB and high-sensitivity CRP levels of the two groups did not differ (Table I). The administration of conventional doses of atorvastatin plus trimetazidine three days before PCI is able to protect PCI patients from myocardial injury.

Recently, Shehata showed that trimetazidine given 72 hours before PCI in diabetic patients with renal dysfunction resulted in a decrease of contrast-induced nephropathy measured by rise in creatinine, and a decrease in myocardial injury measured by rise in cTnl. This could be an effective way of reducing contrast-induced nephropathy during interventions.

Wang showed that biomarker levels above the upper limit of normal were significantly less in patients receiving trimetazidine seven days before PCI (12% vs 23% for CK-MB and 16% vs 35% for cTnl; $P<0.05$ for both). Myocardial infarction determined by CK-MB levels was detected post-PCI in fewer trimetazidine patients than controls (7% vs 12%; $P<0.05$). The benefit of pretreatment was so great that the incidence of periprocedural MI was reduced by nearly 42%. Periprocedural MI, a strong predictor of long-term adverse prognosis, can now be easily reduced and at relatively low cost.

**Biomarkers post–coronary artery bypass graft surgery**

In a prospective, double-blind, randomized, placebo-controlled study, the effects of trimetazidine on the inflammatory response was studied in patients undergoing coronary artery bypass graft surgery (CABG). Interleukin 6 levels were significantly lower in the treatment group compared with control at all time points assessed. This suggests that trimetazidine can reduce the inflammatory response in patients undergoing (CABG).

Reperfusion injury is common during CABG with cardiopulmonary bypass, the critical moment happening at the end of surgery, when there is declamping of the aorta and release of hyperoxic radicals causing the injury. Martins et al studied 60 patients with mild left ventricular dysfunction undergoing CABG, treated with trimetazidine 15 days prior to the procedure. Cardiac troponin T (cTnT) and CK-MB were measured before and 5 minutes after aortic declamping, and 12, 24, and 48 hours later. There was a highly significant difference in favor of trimetazidine showing that it was effective in reducing ischemic reperfusion injury.

**Biomarkers in ischemic cardiomyopathy**

In a study involving 50 patients with ischemic cardiomyopathy, 25 patients were assigned to receive conventional treatment plus trimetazidine. The group receiving trimetazidine demonstrated a reduction in BNP levels (135 ± 22 vs 252 ± 44 pg/mL; $P=0.001$) and cTnT ($P=0.001$), while the control group showed increased plasma BNP levels (288 ± 46 vs 239 ± 59 pg/mL; $P=0.02$), with no change in cTnl levels. Trimetazidine administration also resulted in a significant improvement in exercise tolerance assessed with a 6-minute walk test ($P=0.01$).

<table>
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<th>Group</th>
<th>n</th>
<th>cTnl (pB/ng/mL)</th>
<th>CK-MB (zB/U/L)</th>
<th>∆ MPO (cB/pmol/L)</th>
<th>∆ hs-CRP (pB/mg/mL)</th>
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</thead>
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<td>Control</td>
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<td>38.6±19.5</td>
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<tr>
<td>Experiment</td>
<td>237</td>
<td>0.38±0.52*</td>
<td>25.7±2.6</td>
<td>15.7±26.2*</td>
<td>5.29±8.17</td>
</tr>
</tbody>
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**Table I** Myocardial injury markers and inflammatory markers 24 hours after percutaneous coronary intervention. *P<0.05, compared with the control group.

**Abbreviations:** CK-MB, myocardial creatine kinase; cTnl, cardiac troponin I; MPO, myeloperoxidase; hs-CRP, high-sensitivity C-reactive protein.

Conclusion

A large amount of data is now available to show the beneficial effects of trimetazidine in improving myocardial ischemia, and reducing myocardial necrosis as deduced by a reduction in cardiac biomarkers. This is specially seen when trimetazidine is given preprocedure or as early as possible after the event, as metabolic manipulation shows maximum benefit before permanent myocyte damage occurs. The biomarker improvements have been shown in patients with ACS, both STEMI and NSTEMI with thrombolysis, PCI, or CABG. Importantly, the reduction in ischemic cellular damage as seen by biomarker improvements has translated into clinical benefits for these patients.

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A 62-year-old woman presented to the emergency department with left-sided chest pain and exertional breathlessness. Her past medical history included systemic lupus erythematosus (SLE), chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, and stable angina. She had previously undergone percutaneous coronary intervention (PCI) to her first obtuse marginal (OM1) branch of the circumflex artery. A subsequent angiogram revealed in-stent restenosis in the OM1 of 60% to 70%, without significant functional obstruction based on a fractional flow reserve of 0.82.

On current presentation, her electrocardiogram (ECG) did not reveal any acute ischemic changes; however, her previous cardiovascular history and her symptoms raised the suspicion of non-ST-segment elevation myocardial infarction (NSTEMI). Her highsensitivity cardiac troponin I (cTnI) levels were elevated at 843 ng/L (99th percentile cutoff of 40 ng/L) and she was started on dual antiplatelet therapy. Her renal function was normal. Inpatient coronary angiography was performed; however, no obstructive coronary lesions were identified and she was discharged. Her echocardiogram showed preserved
Abbreviations
CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; cTn: cardiac troponin; LGE: late gadolinium enhancement; MRI: magnetic resonance imaging; NSTEMI: non–ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SLE: systemic lupus erythematosus; OM1: first obtuse marginal

left ventricular function, with no regional wall motion abnormalities.

At routine follow-up she continued to report ongoing chest pain associated with breathlessness and palpitations on minimal exertion. Her medications consisted of doxazosin, isosorbide mononitrate, losartan, ivabradine, amlodipine, aspirin, clopidogrel, atorvastatin, domperidone, hydroxychloroquine, lansoprazole, fluticasone, and salmeterol inhalers. There was limited scope for increasing her antianginal medications, because she had experienced symptomatic hypotension, and 24-hour ambulatory ECG monitoring revealed bradycardia with intermittent pauses of 2.5 seconds.

Dobutamine stress echocardiography showed evidence of reversible ischemia laterally, so coronary angiography was repeated. The repeat angiogram showed de novo lesions in her mid-right coronary artery (Figure 1), for which she underwent PCI and stenting with no significant residual stenoses.

At her follow-up clinic visit she reported ongoing exertional chest pain and also joint problems. Although objectively she had coronary artery disease (CAD), with a previous episode of reversible ischemia, treating this had not fully alleviated her symptoms. In view of her ongoing symptoms and the absence of target lesions on angiography, it was felt that an ischemic episode might not fully explain her symptoms, therefore cardiac magnetic resonance imaging (MRI) was used to further clarify the heart disease.

Cardiac MRI showed normal left ventricular volume and function. Tissue characterization revealed increased T2 signal in anterior apical segments and in inferior and inferoseptal basal segments, in keeping with myocardial edema and inflammation. In addition, there was late gadolinium enhancement (LGE) in the anterior mid-segment of the left ventricle (Figure 2), signifying either myocardial scar or extracellular edema. A repeat cardiac MRI study 6 months later showed no interval change in function and volumes, with homogeneous signal on T2 imaging. The previously noted focal LGE in the anterior mid-segment was unchanged in its extent and transmurality. It was concluded that the myocardial edema could be consistent with a diagnosis of lupus-related inflammatory cardiomyopathy. She was treated medically, and at her latest outpatient visit her symptoms had improved; however, episodes of exertional chest pain remained.

Discussion

Patients with SLE are prone to cardiovascular disease, which develops prematurely, progresses faster, and has more devastating outcomes. Cardiac manifestations of SLE include pericarditis, myocarditis, heart failure, conduction disturbances, noninfective verrucous vegetations (Libman-Sacks endocarditis), premature coronary atherosclerosis, and coronary arteritis.

The primary driver of cardiovascular disease in SLE is thought to be accelerated epicardial coronary atherosclerosis due to persistent systemic inflammation, via autoimmune complement-mediated cytotoxic injury. Lupus myocarditis may also contribute to
the apparent myocardial injury in SLE patients,4 and tends to present with atypical symptoms and cTn elevation. As illustrated by this case, the diagnosis of inflammatory lupus cardiomyopathy can be challenging, especially in older patients with traditional cardiovascular risk factors, where the coexistence of classical CAD and nonischemic inflammatory myocardial injury may lead to cardiovascular injury and confusion over the predominant clinical problem.

Anginal chest pain, with angiographically unobstructed coronaries, is not uncommon in SLE patients and is thought to be due to microvascular coronary obstruction5 causing ischemia. Angiographic findings may therefore be unhelpful and early use of imaging techniques, in particular cardiac MRI, has been shown to add clarity to the diagnosis.6-9 Interestingly, a recent study of patients with cTn-positive chest pain and unobstructed coronaries on angiography, reported that cardiac MRI established the cause for cTn elevation in 65% of cases, most commonly myocarditis (50%), followed by myocardial infarction (11.6%), and cardiomyopathy (3.4%).6 Furthermore, the first report of the European Cardiovascular Magnetic Resonance (EuroCMR) registry revealed that cardiac MRI leads to a change of diagnosis and management in 8.7% of patients.10 There is also evidence for a role for cardiac MRI in acute NSTEMI for diagnosis and prognosis.11

Echocardiography lacks sensitivity to detect myocardial involvement in myocarditis, as the myocardial injury predominantly affects intra- or epicardial function, leading to either apparently normal function or global mild myocardial impairment. Even though endomyocardial biopsy remains the gold standard diagnostic test for myocarditis,12 this is only reserved for severe cases. Because of an epicardial or midmyocardial site for injury, the yield of biopsy in myocarditis is notoriously low. Visualization of myocardial inflammation on cardiac MRI is now an established method to confirm the clinical diagnosis of myocarditis and to follow up on its sequelae.13 Current treatment strategies for lupus-related inflammatory cardiomyopathy involve optimizing treatment of the underlying SLE, which could include corticosteroids and/or immunosuppressive therapy, as well as optimizing treatment for any associated heart failure and CAD.

In this case, the myocardial edema seen on cardiac MRI, angiographically unobstructed coronaries at presentation, and ongoing symptoms despite later revascularization were not typical of NSTEMI. The myocardial LGE in this patient could represent infarcted tissue, related to the previous coronary intervention. However, in nonischemic cardiomyopathy the location of LGE within the mid-wall of the left ventricle has been associated with an infectious or inflammatory pathology.14 This case illustrates the need for complementary information, to help understand the source of cardiovascular injury, in patients with both CAD and suspected myocarditis, in whom acute coronary syndrome is not confirmed. This may require advanced phenotyping, for example, by using cardiac MRI.

This present case also illustrates the importance of taking into account coexistent medical conditions when interpreting cTn results. With the routine use of high-sensitivity cTn assays in early rule-out protocols for NSTEMI, chronic cTn elevations may be detected in many other conditions, including chronic heart failure,15 stable CAD,16 atrial fibrillation,17 chronic renal failure,18 COPD,19 and sepsis,20 and in healthy persons with cardiovascular risk factors and/or advanced age.21 The list of conditions that can cause elevated cTn is extensive and can represent a diagnostic challenge when patients present with coincident chest pain and a history of coronary intervention.

**Conclusion**

Cardiac involvement in SLE is common and often unsuspected. In this case, elevated high-sensitivity cTnI in the absence of target lesions on angiography and persistent symptoms after successful treatment of obstructive coronary lesions led us to think that the symptoms were not fully explained by ischemia. Cardiac MRI was crucial in highlighting an alternative diagnosis. In patients with elevated cTn, symptoms of chest pain and breathlessness, and absence of obstructive coronary disease, cardiac MRI should be considered early to exclude inflammatory cardiomyopathy.

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The evolution of the criteria to define myocardial infarction

The criteria to define myocardial infarction (MI) have been modified several times over the last decades, and this has had important clinical, epidemiological, and research implications. The aim of this review is to summarize the evolution of the diagnostic criteria of MI and the consequences of these changes on clinical management.

The first guidelines to define MI were published by the World Health Organization (WHO) in 1959 (Figure 1). A revision, the first universal definition of MI, followed in 1979. These guidelines emphasized the presence of two of three possible criteria: clinical symptoms compatible with MI, typical electrocardiography (ECG) changes, and elevated circulating biomarkers of myocardial injury, which at that time were mainly total creatine kinase (CK) and myocardial CK (CK-MB).

Following the introduction of cardiac troponin (cTn) into clinical practice, it soon became clear that “unstable angina” patients, ie, those with normal CK-MB, had an increased cardiac risk if cTn was elevated. Considering this issue, together with concerns over the limited cardiospecificity of CK-MB, the National Academy of Clinical Biochemistry (NACB) issued, in 1999, the first guidelines for the use of cardiac markers in acute coronary syndrome (ACS) that included cTn. At that time, two cutoff values were suggested: the 97.5th percentile of a healthy reference population to define unstable angina with minimal myocardial injury, and a receiver operator characteristics (ROC) curve–derived cutoff for definite MI. However, this approach maintained at its core the insensitive and nonspecific criteria

Keywords: definition criteria; diagnosis; myocardial infarction; troponin
Defining acute myocardial infarction predicated on CK-MB and was, especially from today’s perspective, suboptimal.

In 2000, the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC) Committee redefined the diagnostic criteria of MI. Given its superior sensitivity and specificity, cTn was recommended as the biomarker of choice with a significant rise and/or fall in serially measured concentrations and at least one value above the 99th percentile. In addition, the presence of either ischemic symptoms, ischemic ECG changes, or coronary artery intervention was required. Importantly, these criteria lowered the diagnostic cTn concentration cutoff from a ROC-derived value and increased it from the 97.5th percentile recommended by the NACB. The 99th percentile was chosen as it is approximately three standard deviations from the mean, which was thought to protect against false-positive values. The ESC/ACC Committee also stated that the acceptable imprecision at the 99th percentile should be ≤10%, because of concerns regarding the analytic variability in biochemical determinations.

The ESC/ACC consensus document had several major clinical implications. First, the use of cTn levels became the cornerstone of the diagnosis of MI. Second, the increased sensitivity of cTn relative to CK-MB resulted in a 30% to 80% increase in the prevalence of MI and a more reliable identification of at-risk patients in need of more aggressive therapies. Finally, the call for rigorous and high analytical precision has driven assay technical development.

Subsequently, the ESC/ACC Committee was expanded to include representatives from the American Heart Association and World Heart Federation. In 2007, this task force updated the universal definition of MI. Again, a combination of clinical symptoms, cardiac biomarkers (preferably cTn), and ischemic ECG changes were central to the definition of MI. However, because of pathological, clinical, and prognostic differences, several subtypes of MI were defined. Type 1 MI is caused by a sudden rupture of a coronary plaque. Type 2 MI, which accounts for up to 25% of all MI, is secondary to a myocardial oxygen supply/demand imbalance due to tachycardia, hypertension, etc, with or without underlying coronary artery disease. Also included in this category are patients who might have coronary endothelial dysfunction or vasospasm. Type 3 MI is the result of coronary thrombosis with sudden death before biomarker results are available. Type 4 MI is caused by complications of percutaneous coronary intervention (PCI): type 4A is a periprocedural MI, while type 4B is related to stent thrombosis. Type 5 MI is related to complications of coronary artery bypass surgery.

Interestingly, the universal definition did not considerably affect the prevalence of MI. However, the introduction of high-sensitivity cTn assays in the early 2010s resulted in a shift from unstable angina to MI and an increased prevalence of low-level cTn elevations in the setting of ischemic imbalance and critical illnesses (ie, type 2 MI). This was considered in the third universal definition of MI from 2012. In this revision, the classification into five MI subtypes was retained (Table I). What was new was the introduction of the term myocardial injury, meant as an increase in cTn in nonischemic conditions such as acute ventricular stretch (Figure 2). Also, type 4A MI was defined more stringently, ie, by an elevation of cTn values >5 times the 99th percentile within 48 hours after PCI together with clinical or ECG criteria. The cTn cutoff was chosen acknowledging that small, not necessarily prognostically adverse, cTn elevations may be detected even after uncomplicated PCI. Similarly, the cTn cutoff to define type 5 MI was raised from 5 to 10 times the 99th percentile within 48 hours, acknowledging that biomarker elevations may occur as part of the surgical procedure itself. Finally,
A new category of type 4C MI (MI due to restenosis ≥50% after an initially successful PCI) was created for reporting in clinical trials. The evolution of the definitions of MI from rather simple criteria in the first WHO documents toward a differentiated five-category classification would not have been possible without medical and technical improvements. In particular, the availability of more sensitive and cardiospecific biomarkers has had a clear impact in this regard, but also the increasing use of invasive treatment strategies and a more differentiated perspective on the pathophysiology of myocardial injury. This has contributed to a better classification of patients, which, for example, is illustrated by the improved identification of cTn-positive high-risk acute coronary syndrome (ACS) following the introduction of the ESC/ACC criteria in 2000.6-9 Another example of improvement is the MI classification introduced in the 2007 universal definition.10 With this, it has become clear that type 2 MI is not a benign epiphenomenon in the setting of illnesses other than ACS, but rather an indicator of myocardial vulnerability and increased risk.11

Steps ahead

Still, several aspects of the criteria to define MI are far from settled and there is much discussion regarding this. Below are listed some of the issues that are debated and might be subject to modification in the forthcoming updates of the universal definition:

1. There is a need to define the cTn cutoff in a more precise manner. The currently recommended 99th percentile lacks biological plausibility since cardiovascular risk is continuous and starts to rise at concentrations below this dichotomous cutoff.16 In addition, the 99th percentile is highly dependent on the composition of the population from which it is derived,17 which is the reason why corrections for age, gender, and/or race may be needed. In part, this could be mitigated if the populations used to derive the 99th percentile were defined and standardized.

2. The universal definition does not suggest criteria to define a significant change in cTn levels. Absolute
changes usually provide greater diagnostic utility than relative changes, but baseline concentrations and the biologic variability of cTn need to be taken into account.

3. The universal definition recommends cTn measurements at presentation and after 3 to 6 hours, but shorter sampling protocols using high-sensitivity assays have been suggested for ruling out MI. On the other hand, cTn levels may increase late, which is the reason why sampling at >6 hours could be necessary if there is a high index of clinical suspicion.

4. The distinction between type 1 and type 2 MI may be challenging and requires careful judgment as the approaches to clinical management are different. In many cases, where there is a clear non-ACS-related cause of myocardial ischemia, eg, hypotension due to perioperative bleed, this distinction is not difficult. However, it may be complicated in other conditions, eg, cTn increase in acutely decompensated ischemic cardiomyopathy. This is a common source of anxiety among clinicians. Often, a subsequent test for inducible ischemia is helpful to decide whether there is underlying coronary artery disease or not, and to guide treatment and follow-up.

5. Even the distinction between MI and myocardial injury may cause problems. In general, a diagnosis of MI should not be made if the clinical setting is not of acute ischemia. However, there are conditions in which multifactorial causes for cTn elevation may exist, eg, septic shock with hypotension in a patient with known coronary artery disease. Nevertheless, the distinction between type 2 MI and myocardial injury with necrosis usually has less immediate therapeutic implications.

6. As outlined above, the cTn cutoffs to define type 4 and type 5 MI have been modified in the third universal definition. As biomarker elevations may occur as part of the interventions themselves, the discussion on this topic will likely continue.

Summary and outlook

The evolution of the criteria to define MI has had a major impact on the clinical management of patients with ACS. Still, there are issues that need further discussion and clarification. Further work is also required in relation to appropriate diagnosis-related coding so that different types of MI can be reimbursed accordingly. It is thus evident that the diagnostic classification of patients with ACS is dynamic and will likely continue to evolve.

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Cardiac biomarkers have a central role in the diagnosis of an acute coronary syndrome (ACS). Recently, molecules such as heart-type fatty acid–binding protein (H-FABP), pro-substance P, and mast cell–derived tryptase, have been suggested to be superior to creatine kinase (CK)–MB or cardiac troponins in the early detection of ACS. However, their role has not been confirmed in clinical studies. On the other hand, the role of troponin testing has been repeatedly validated, with such awareness unintentionally leading to the overuse of the test. Measurements are often performed among those patients without symptoms suggestive of ACS, thus reducing the specificity of the test. Nonetheless, when troponin levels are interpreted with clinical findings and electrocardiogram results, the diagnosis of ACS is highly accurate.

Corroboration or exclusion of a diagnosis of ACS remains a critical step in the management of patients presenting with chest pain. Treatment strategies of those patients diagnosed with ACS are dictated by multiple international guidelines and have been shown to significantly affect prognosis. However, given the burden of established cardiovascular (CV) disease, risk reduction strategies are assumed to confer a major benefit. In this regard, the Framingham risk score represents the most popular clinical tool for the estimation of CV risk. However, while there is an established power of the Framingham risk score in predicting obstructive coronary artery disease, the majority of acute CV events occur in individuals who are stratified as having low to intermediate risk. In line with these considerations, stenosis severity is also a poor predictor of plaque rupture. As such, there is an increasing need to develop specific markers that predict future ACS.

ACS is accompanied by an intense inflammatory response, and an interplay between the inflammatory and thrombotic systems has been proposed to be a key regulator of ischemic vascular events. Activated platelets bind to circulating leukocytes and recruit them to sites of vascular injury and thrombus. For this reason, circulating biomarkers of inflammation such as C-reactive protein (CRP), have represented the subject of many recent clinical studies. However, CRP measurements have been shown to confer only a modest predictive power for future cardiovascular events.

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) is an imaging modality that allows identification of small, metabolically active tissues such as tumors and inflamed lesions, by quantification of ¹⁸F-FDG uptake. In the cell, ¹⁸F-FDG, an analogue of glucose, is phosphorylated to FDG-6-phosphate by hexokinase and adenosine triphosphate (ATP), a rate-limiting step in glycolysis. FDG-6-phosphate is not metabolized further in the glycolytic pathway, so it remains trapped inside the cell, in a process called “metabolic trapping.” Recently published studies have tested this technique in the CV research field. An increased ¹⁸F-FDG uptake has been documented in activated proinflammatory macrophages, which play a major role in arterial plaque destabilization and consequent clinical manifestation of ACS. The significance of such findings has been further evaluated in prognostic studies, with
increased arterial 18F-FDG PET signals being inversely associated with the timing of acute CV disease manifestation. In addition, assessment of the metabolic activity of the spleen, a much earlier marker of inflammation, independently predicted the risk for subsequent CV events. Other studies have combined PET and computed tomography (CT) signals, and have shown that the link between the PET/CT signal and CV events is independent of the effects of coronary artery calcium score on both CV outcomes and arterial inflammation. To further support these findings, there are studies that have demonstrated that arterial 18F-FDG uptake is reduced by statins and by drugs that are thought to inhibit inflammatory pathways.

In conclusion, the advent of specific biomarkers, such as cardiac troponins, has progressively increased our ability to diagnose an ACS. Following diagnosis, treatment strategies for patients with an ACS are also well standardized and proven to positively impact prognosis. However, the majority of acute CV events occur in patients deemed to have low to intermediate risk, thus suggesting that an intervention at this level (prediction/prevention of acute CV events) could have a potentially relevant impact.

As mentioned, platelet-leukocyte interactions offer an important mechanistic link between the inflammatory and thrombotic systems. The information provided by the 18F-FDG PET signal appears to be distinct from that provided by circulating biomarkers of inflammation, which carry information from both vascular and nonvascular sources. Indeed, metabolic biomarkers appear to allow for the circumscription of a weak, systemic inflammatory disease that ultimately leads to acute CV events. Large clinical studies are needed to confirm such results.

REFERENCES

**Accuracy**
Accuracy is a measure of the agreement/closeness of a measured value to the true/actual value. With respect to diagnostic accuracy measures, the area under the receiver operating characteristic (ROC) curve can be used as a measure of the accuracy of a diagnostic test.

**Negative predictive value**
Negative predictive value, with respect to diagnostic testing, is a conditional probability describing the proportion of patients with a negative test that are free of the target disease. Negative predictive value of a diagnostic test is calculated as a ratio: true negative value/(true negative value + false negative value).

**Positive predictive value**
Positive predictive value, with respect to diagnostic testing, is a conditional probability describing the proportion of patients with a positive test that are positive for the target disease. Positive predictive value of a diagnostic test is calculated as a ratio: true positive value/(true positive value + false positive value).

**Precision**
Precision is a measure of the reproducibility of a measurement. Precision represents the closeness of agreement between independent measurements, and is commonly expressed as a coefficient of variation or standard deviation.

**Receiver operator characteristic**
Receiver operator characteristic (ROC) is a graphical plot that highlights a binary classifier system’s performance amidst varying discrimination thresholds. Plotting the true positive rate against the false positive rate at several threshold settings will result in the generation of an ROC plot.

**Sensitivity**
Sensitivity is also known as “true positive rate,” and is a statistical measure of the performance of a binary classification test, which measures the percentage of actual positive outcomes/end points that are correctly identified as being a positive outcome/end point, hence the “true positive rate.”

**Specificity**
Specificity is also known as “true negative rate,” and is a statistical measure of the performance of a binary classification test, which measures the percentage of actual negative outcomes/end points that are correctly identified as being a negative outcome/end point, hence the “true negative rate.”
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