The development of highly sensitive assays for cardiac troponin T (hs-cTnT)4 and cardiac troponin I (hs-cTnI) represents the latest technological advance in a field that has witnessed continual progression toward more sensitive and more precise tools for detecting cardiac injury. The hs-cTnT assay, for example, can detect cTnT concentrations 10-fold lower than the current fourth-generation assay, with high precision at the myocardial infarction (MI) detection limit. Despite the potential for such evolution to improve patient care, clinicians, including practicing cardiologists, often find themselves poorly prepared for the introduction of more-sensitive assays, because they fail to consider the implications of increasing sensitivity on the interpretation of the test results. We believe that highly sensitive troponin assays offer new opportunities to improve cardiovascular health, but they also present challenges in the areas in which troponin testing is most commonly used today.

**Terminology**

Although it may seem natural to use the terminology “high-sensitivity troponin T (hs-cTnT) or troponin I (hs-cTnI)” in a manner similar to high-sensitivity C-reactive protein (hs-CRP), we discourage this approach and strongly recommend that “highly sensitive” or “sensitive” be used to describe the assay only and not the biomarker. The highly sensitive assays measure the same protein as the standard assays, and even more sensitive cardiac troponin assays will certainly be developed, thus making any “high sensitivity” designation obsolete.

**New Opportunities and Indications for Troponin Testing**

The ability to detect concentrations of circulating troponin in the single-digit nanogram-per-liter range has expanded the potential applications of troponin testing in new directions, including in the ambulatory setting. For example, using research versions of the hs-cTnT assay, investigators from the Valsartan Heart Failure Trial (Val-HeFT) and Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trials demonstrated cTnT to be detectable at very low concentrations in nearly 100% of patients with stable chronic heart failure or chronic coronary artery disease; moreover, increasing concentrations of cTnT still well below the detection limit of standard cTnT assays were associated with progressively higher rates of death and heart failure progression or development (1, 2).

Population screening with cardiac troponins had previously been thought to be impractical, given the very low prevalence of detectable troponin in the general population with standard assays (3). Recently, however, the hs-cTnT assay has been explored as a potential screening tool to identify asymptomatic individuals who are at risk for cardiovascular disease. In the Dallas Heart Study, cTnT was measured with both standard and highly sensitive assays in 3593 adults between 30 and 65 years of age. The prevalence of detectable cTnT (≥3 ng/L) with the highly sensitive assay was 25%, compared with 0.7% for the standard assay (4).

In the Cardiovascular Health Study, which studied 4221 adults ≥65 years of age (5), and the Atherosclerosis Risk in Communities Study, which included 9698 participants between 54 and 74 years of age (6), the prevalence of detectable cTnT with the hs-cTnT assay was 66.2% and 66.5%, respectively. Concentrations of cTnT in the population were higher among older individuals, males, and African Americans. A clear adverse cardiovascular phenotype associated with higher cTnT concentrations, with measures of structural heart disease including left ventricular hypertrophy, left ventricular systolic dysfunction, as well as chronic kidney disease, increasing markedly across categories of higher cTnT concentrations. Of interest is that the association of cTnT with measures of atherosclerosis burden was...
much less robust (4). This finding is supported by observations from the PEACE trial, which found cTnT to be associated strongly with death and heart failure events but not with myocardial infarction, even though the PEACE trial had enrolled individuals with chronic coronary artery disease and preserved left ventricular systolic function (2).

In each of the 3 large population-based studies, higher cTnT concentrations measured with the hs-cTnT assay were strongly associated with an increased risk for all-cause and cardiovascular disease mortality (4–6). Similar findings were seen with regard to incident heart failure. These associations remained significant after adjustment for traditional risk factors, as well as for renal function and concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hs-CRP. The addition of cTnT augmented the performance of traditional risk-prediction models, such as the Framingham Risk Score, improving discrimination and risk classification. When cTnT as measured with highly sensitive assays was compared directly with NT-proBNP and hs-CRP, cTnT performed at least as well as NT-proBNP and clearly outperformed hs-CRP (4–6). Although an independent association with coronary heart disease events was observed, this association was considerably weaker than the associations seen for death and heart failure events (6).

In the Cardiovascular Health Study, a second measurement of cTnT was performed 2–3 years after the baseline measurement in approximately two-thirds of the cohort. Regardless of the baseline cTnT concentration, an increase in cTnT by ≥50% was associated with a subsequent increased risk of death and heart failure, whereas a decrease by ≥50% was associated with lower risk (5). This finding is important because it suggests that risk reflected by cTnT concentration may be modifiable.

**Next Steps in the Transition of Troponin Testing to the Physician’s Office**

In aggregate, these results suggest that the chronic release of very low concentrations of cardiac troponins is common among asymptomatic adults and, when detected, identifies individuals who may have unrecognized structural heart disease and an unexpectedly high risk of heart failure and cardiovascular death. Although these early findings offer promise that highly sensitive troponin assays may provide a relatively inexpensive tool for office-based screening, more work needs to be done before routine testing can be recommended. First, it will be necessary to identify lifestyle factors or drug treatments that can modify the risk associated with low-level increases in troponins; ideally, such treatments would also reduce the troponin concentration so that serial testing could be used to monitor the effectiveness of the intervention. Additionally, studies with longer follow-up times will be necessary to determine whether all detectable troponin values are associated with risk or whether there is a “normal” threshold below which cTnT concentrations carry minimal risk. Whether such thresholds vary with age, sex, and other clinical characteristics will also need to be clarified, along with the influence of transient acute medical conditions that may or may not carry the same link with long-term risk.

We believe that it is unlikely that a uniform therapeutic response will be appropriate for all individuals with detectable concentrations of circulating cardiac troponin. Although structural heart disease and chronic kidney disease appear to explain some of the variation in troponin concentration in the population, many other known and unknown factors contribute as well. In the ambulatory setting, troponins may function as relatively nonspecific markers of “end-organ damage,” with concentrations reflecting the final common pathway of multiple different pathways to chronic cardiac injury. The absence of a specific biological pathway leading to troponin release may hinder the use of troponins as a trigger for a particular treatment response in this setting. A more likely algorithm would be for the troponin value to prompt additional testing, likely with cardiovascular imaging (focusing on structural heart disease rather than atherosclerosis), to identify the source of chronic cardiovascular injury and to target therapy based on the presumed mechanism of injury. With advances in ultrasound technology, it may soon be possible to perform a handheld echocardiogram in a physician’s office as a response to a “positive” result for a highly sensitive troponin assay (7). Although a troponin measurement is inexpensive, the impact and cost of downstream testing, particularly cardiovascular imaging, will need to be assessed prior to implementation of a screening strategy (8). At this time, the American College of Cardiology Foundation/American Heart Association guidelines for assessing risk in asymptomatic adults do not recommend biomarker assessment; however, highly sensitive troponin assays were not considered in this guideline (9).

**Interpreting Sensitive Troponin Assays in the Emergency Department Setting**

Several recent studies have evaluated the performance of sensitive troponin assays for MI detection in the emergency room (10, 11). These studies demonstrated improved discrimination of MI events with the more sensitive assays, particularly in the early hours after symptom onset, in populations selected according to
the probability of myocardial ischemia for evaluation in specialized chest pain units. The improvement in the area under the ROC curve was due to the improved sensitivity of the new assays, which overcame worsening in specificity. Despite the relatively encouraging results of these studies, many cardiologists view these findings with considerable trepidation.

Although the negative predictive values of the more sensitive assays are evident from these studies, with the consequence that more patients may be able to be sent home sooner, the decrement in the positive predictive value has implications for the cardiology community. Few topics cause more consternation among cardiologists than the “troponin consult,” which is a consult to a cardiologist to provide interpretation of an abnormal troponin value in a patient without clear symptoms or concomitant evidence of acute ischemia. Such consults are actually now mandated in the VA Health Care system for all positive troponin values. These consults are challenging because even when the various potential causes of ischemic and nonischemic myocardial injury are considered, frequently no clear attributable cause can be found for the troponin increase. Moreover, the consulting cardiologist often perceives such consults as an explicit transfer of medico-legal liability from another provider [i.e., the emergency department (ED) or the primary-care team] to the cardiologist.

Given the prevalence data described above, at least 60%–70% of individuals presenting to an ED with chest symptoms on a daily basis will have measurable troponin concentrations. Moreover, among patients observed in a chest pain unit, it will be common for troponin concentrations to be above the MI-detection threshold chronically, because such patients typically have either known coronary disease or multiple risk factors. For example, in a study of chest pain patients by Januzzi et al., 16.4% of patients had cTnT values \( \geq 13 \text{ ng/L}, \) despite an MI rate of only 2.1% (12). These observations highlight the need for a paradigm shift regarding the interpretation of troponin values. Whereas troponin results have classically been interpreted solely as dichotomous tests (positive/negative), there may now be a rationale to consider interpretation on a continuous scale.

Bayesian principles need to be considered when interpreting the highly sensitive troponin assays for MI detection. In the typical chest pain observation unit in the US, which does not admit individuals with clear or probable acute coronary syndrome, the probability of MI is low, typically <5%. With such a low pretest probability of MI, the balance between detecting an MI that would have been missed with a standard assay and detecting myocardial injury due to something other than MI will tip markedly toward increased “false positives” (Table 1). Thus, appropriate interpretation of troponin results with the highly sensitive assays will necessarily require a shift back to a global assessment of the clinical probability of myocardial ischemia that is inherently more demanding than simply interpreting troponin results as positive or negative. Additionally, we suspect that many ED providers will be uncomfortable managing the patient with a detectable troponin value that is below the MI-decision limit. If such individuals are routinely referred for cardiology consultation and/or additional testing, the indirect costs (and potential harms from unnecessary testing) associated with the highly sensitive assays may be substantial.

There are, of course, also potential advantages of the highly sensitive assays in the ED setting. Improved precision of these assays at the MI-detection threshold should improve MI classification. Although most of the detectable troponin values below the 99th percentile value will represent “baseline” concentrations reflective of chronic injury, concentrations in this interval appear to identify an adverse prognosis in patients.

### Table 1. Additional cTnT values above the MI-detection threshold with a highly sensitive (hs) cTnT assay, compared with a standard cTnT assay, across differing MI probabilities in the target population.a

<table>
<thead>
<tr>
<th>MI probability</th>
<th>Positive tests with standard assay, /1000 patients</th>
<th>Positive tests with hs assay, /1000 patients</th>
<th>Additional positive tests with hs assay vs standard assay meeting MI definition, /1000 patients</th>
<th>Additional positive tests with hs assay vs standard assay not meeting MI definition, /1000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>17%</td>
<td>199</td>
<td>328</td>
<td>21</td>
<td>108</td>
</tr>
<tr>
<td>10%</td>
<td>146</td>
<td>275</td>
<td>12</td>
<td>117</td>
</tr>
<tr>
<td>5%</td>
<td>108</td>
<td>237</td>
<td>8</td>
<td>121</td>
</tr>
<tr>
<td>3%</td>
<td>93</td>
<td>222</td>
<td>3</td>
<td>126</td>
</tr>
</tbody>
</table>

a Data from Reichlin et al. (10) were used for the base-case MI prevalence (17%) and for sensitivity and specificity for the assays. These sensitivity and specificity data at presentation were used to calculate the positive test rate at various MI probabilities. The threshold values used to define a positive test result were the limit of detection for the standard assay and the 99th percentile value for the hs-cTnT assay.
with acute coronary syndrome (13), and this information may improve risk assessment in the ED. Prospective studies are needed in chest pain populations at lower risk to determine whether detectable concentrations of troponin below the MI threshold identify individuals at increased risk for short-term adverse events and whether cost-effective strategies for additional evaluation can be defined. Finally, it is also possible that serial increases in troponin concentrations with values that remain below the MI-detection threshold will help to identify acute coronary ischemia earlier, prompting earlier intervention and preventing additional myocardial injury. This hypothesis, however, although attractive, has yet to be proved. A major research priority is to establish whether serial changes in troponins can solve the clinical “specificity problem” and discriminate acute cardiac injury due to coronary ischemia from acute injury caused by other processes and from chronic injury.

Conclusions

It is clear that the highly sensitive troponin assays will present new challenges in the ED and at the interface between the ED and the cardiology consultant. With the adoption of highly sensitive assays for MI detection, we believe that there is a need for the development of algorithms for interpreting detectable troponin values that are below the MI threshold, together with recommendations for additional testing and referral for patients with an increased cardiac troponin concentration and a low clinical suspicion for acute coronary syndrome. In contrast, the application of highly sensitive troponin assays in the ambulatory setting appears to be an attractive approach to enhance primary and secondary prevention, with fewer negative implications. In this setting, the detection of very low troponin concentrations identifies risk not captured with other tools. It is hoped that future studies will clarify the clinical value and identify the best approach to incorporating these assays for population screening.

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References