

EDITORIAL COMMENT

# What to Expect When Measuring High-Sensitivity Troponin

## Practical Advice for Clinicians\*

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*Everything must be made as simple as possible.  
But not simpler.*

—Albert Einstein (1)

The path to the high-sensitivity cardiac troponin (hs-cTn) assays has taken more than 2 decades. Historically, after early studies showing superior diagnostic and prognostic performance compared with creatine kinase isoenzymes, conventional cTnI and T were adopted as gold standard biomarkers to evaluate patients with suspected acute coronary syndrome (ACS). Subsequently, work by the Third Global Myocardial Infarction Task Force (2) and others began to focus on exactly what defined an abnormal cTn, recognizing that ACS patients experienced a worse prognosis at cTnI or T concentrations below these biomarkers' reference limits for myocardial infarction (MI) diagnosis. Indeed, any measurable cTnI or T in the context of an ACS appeared to portend a worse prognosis (3), suggesting the need to reconsider reference ranges for both biomarkers. Accordingly, consensus developed that upper reference limits for cTnI or T should be predicated on the 99th percentile of a healthy normal population (2).

However, an important conundrum existed: although the risk of ACS complications appears at very low levels of cTnI or T, such concentrations

produced unacceptably high imprecision in conventional cTnI or T assays. Thus, the need existed for cTn assays with greater precision at low analyte concentrations; this ultimately led to development of hs-cTn methods.

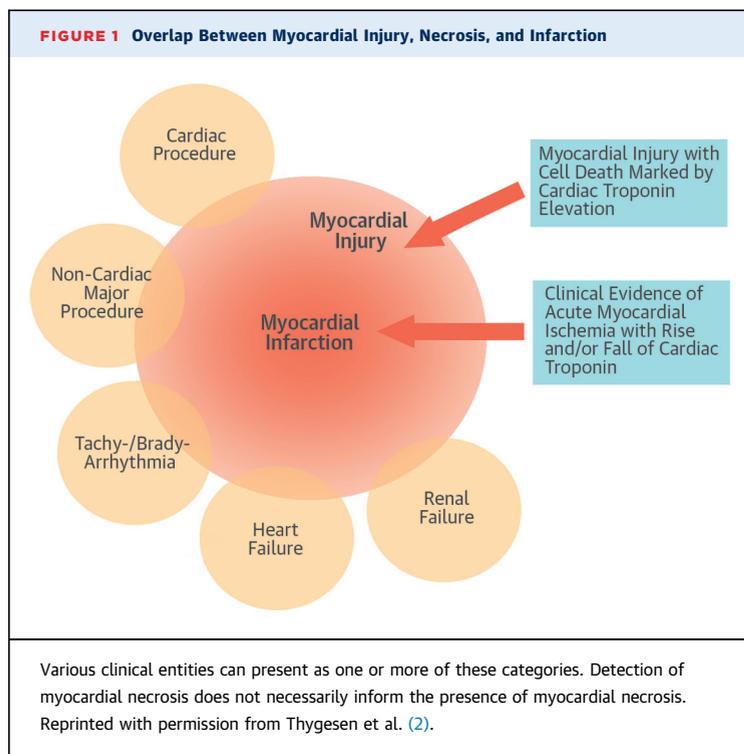
The hs-cTn immunoassays are frequently based on the same antibodies used in conventional cTnI or T assays, but, through changes in how the assays are run, allow precise detection of very low concentrations of cTnI or T. When testing blood samples of normal, healthy individuals (where conventional methods are routinely negative), hs-cTn methods may detect a signal in a majority of these individuals and can do so with high precision at the 99th percentile of a normal population.

In patients with acute MI, hs-cTnI or T are often abnormal earlier than conventional cTn methods, allowing for more rapid diagnostic evaluation (4-6); as soon as 2 h after presentation, a substantial percentage of patients can be evaluated accurately with hs-cTn. Additionally, hs-cTn assays detect acute MI in up to 25% of ACS patients with normal conventional cTn values who are thought to have unstable angina (UA). Beyond its enhanced diagnostic sensitivity, hs-cTn has also been proven superior to conventional cTn for prognosis. Thus, hs-cTn methods represent a major advance.

However, in laboratory medicine, when a test has enhanced sensitivity, the risk of loss of specificity increases. Indeed, with improved sensitivity, hs-cTn methods now detect previously unrecognized myocardial necrosis in many acute and chronic cardiovascular conditions, confounding interpretation and confusing clinicians (Figure 1). Make no mistake, such abnormal values reflect myocardial injury, but the clinician is faced with important questions: Are these values due to an acute MI? Or do they arise from some other cause of myocardial injury, such as heart

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Specifically focusing on the 10,476 patients with an hs-cTnT between the 99th percentile of 14 ng/l and 50 ng/l (a group that would have been called troponin negative using conventional cTnT methods), hs-cTnT reclassified 18.2% from UA to acute MI, revealing the incremental sensitivity of hs-cTnT. However, most patients with an abnormal hs-cTnT did not have an acute MI, raising justifiable concerns about the ramifications of lower specificity for the diagnosis. Are these false positives? Perhaps, from the point of view of an acute ischemic coronary event, but clearly such low level hs-cTnT increases are not benign: the SWEDEHEART investigators demonstrated very simply but elegantly that the risk of mortality began to increase right above the threshold of 14 ng/l, regardless of diagnosis, and prognosticated well in women as well as elderly patients. Thus, irrespective of an MI diagnosis, patients with an abnormal hs-cTnT value are indeed at higher risk and should be considered as such.

Caveats for this analysis clearly exist. First, this is a highly selected population of higher risk patients admitted to specialized coronary units with a high likelihood of an ACS diagnosis. Indeed, in this analysis, of those below the hs-cTnT detection limit of 6 ng/l (which some suggest identifies an ultralow-risk population), 2.2% of 5,790 patients received a diagnosis of acute MI (something the investigators do not explain), whereas an additional 28.3% had a diagnosis of UA, a finding that contradicts the growing belief that ultralow hs-cTn values predict a low rate of ACS (4,5). The analysis used the highest recorded hs-cTnT value rather than considering serial measurements; seeking a significant increase and/or decrease in hs-cTn has been suggested to best inform the presence of acute MI, whereas more chronic increases without a change in serial measurement may be seen in non-ischemic syndromes.

What's a clinician to do then? On the one hand, we have a tool with substantially greater sensitivity to diagnose acute MI and with outstanding ability to predict a poor prognosis. On the other hand, these assays detect myocardial necrosis from other disease states and conditions, so specificity for acute MI may be challenged.

It is critical for physicians to remember that an abnormal hs-cTnI or T value only informs the presence of myocardial necrosis, not its mechanism; clinicians must carefully consider the differential diagnosis for an abnormal hs-cTn value just as they do for abnormal values of other diagnostic tests and only make a diagnosis of acute MI if evidence of myocardial ischemia is present. As noted, serial measurement over a short period of time may be

failure-related subendocardial injury? If a patient does not obviously have an acute MI but has increased hs-cTn, is this even important?

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In this issue of the *Journal*, investigators from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry addressed these questions (7); in this analysis, 48,594 patients with symptoms suggestive of ACS admitted to a coronary intensive care unit or specialized unit were studied. Of these patients, 47.3% had an acute MI, whereas 23.2% had UA. The investigators divided subjects into 4 groups based on their maximal hs-cTnT value during hospitalization: those with hs-cTnT below the detection limit of 6 ng/l, those with hs-cTnT between 6 and 13 ng/l (measurable, but normal), those with hs-cTnT above the 99th percentile of 14 ng/l but below 50 ng/l (abnormal by hs-cTn standards, but below the level where a conventional cTn would be abnormal), and then  $\geq 50$  ng/l (a range where both hs-cTnT and conventional cTnT are abnormal). Notably, across these categories, clinical risk factors, demographics, extent of disease, and severity of presentation worsened: with each increase in hs-cTnT came a parallel increase in medical complexity and clinical risk.

informative regarding rapid increases and/or decreases in hs-cTn characteristics of acute MI. Considering hs-cTn as a quantitative rather than qualitative measure will be important, too: the days of a patient being referred to as “troponin positive” should end, and clinicians should now consider the potential diagnoses seen in the hs-cTn range detected. Finally, determining the appropriate workup for patients with abnormalities in hs-cTn values will be necessary. Yes, there will be more testing and treatment done in these patients, but in theory, thanks to the focus drawn to them through recognition of an abnormal hs-cTn value, such management will likely be more cost-effective given the higher risk status of such patients and may well lead to improved outcomes.

There will be a learning curve as we gain experience with hs-cTnI or T. It is reasonable to expect that the advent of hs-cTn testing will inevitably be accompanied by growing pains; some may call for the simpler paradigm afforded by conventional cTn. In this case, however, simpler is not better: more rapid and sensitive detection of acute MI coupled with greater prognostic value from hs-cTn testing makes it worth the effort to become acquainted with its use.

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