The Era for High-Sensitivity Cardiac Troponin Has Begun in the US (Finally)

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On January 19, 2017, the Food and Drug Administration (FDA)[3] announced the clearance of Roche Diagnostics Gen 5 STAT cardiac troponin T assay in the US (*1*). This is the first of what is likely to be many next-generation or perhaps high-sensitivity (hs) cardiac troponin (cTn) assays released in the next few years. The Roche Diagnostics Gen 5 assay has been available in Europe, Asia, Australia, and Canada for 7 years. The 99th percentile cutoff limit has been changed from <0.010 ng/mL (10 ng/L) for the 4th generation cardiac troponin T (cTnT) assay to sex-specific cutoffs of 14 ng/L (0.014 ng/mL) for women, 22 ng/L (0.022 ng/mL) for men, and 19 ng/L (0.019 ng/mL) for both sexes for the 5th generation. (Note: a value of 10 ng/L with the 4th generation assay will read closer to 30 ng/L with the 5th generation assay.) As with assays for other analytes, each hospital may need to establish their own sex-specific cutoffs based on their study population. Use of this assay and cutoffs will enable an earlier detection and rule-out of acute myocardial infarction (AMI) of patents who present to the emergency department (ED) with AMI signs and symptoms and detect more patients at risk for future adverse cardiac events. One immediate consequence of implementing hs-cTn assays will be the conversion of reporting units from nanograms per milliliter to nanograms per liter, which enable reporting of values to whole numbers (*2*). Many believe that reporting whole numbers will decrease the opportunity for error for interpreting cTnT values.

Many of our colleagues in laboratory medicine, EDs, and cardiology have questioned the need and value for an hs-cTn assay and use of low values for the 99th percentile cutoff limit. The opponents to hs-cTn assays argue that implementation will greatly diminish the clinical specificity for diagnosis of AMI by detecting more patients who have mild increases in cTn concentrations (*3*). This notion is correct if cTn is considered only as a marker of acute coronary syndromes. However, it is important to note that cTn is a heart-specific biomarker, not a disease-specific biomarker. Thus, to fully understand the value of cTn, one must consider cTn as a marker of cardiac injury, not just ischemic damage from an AMI. In this context, increased results are highly specific for this condition. In fact, the assignment of a laboratory test to just a single medical indication is atypical. For example, an increase in the liver enzyme alkaline phosphatase is a powerful indicator of obstructive liver disease, but does not allow a hepatologist to necessarily indicate the presence of gallstones. Optimum use of hs-cTn for the diagnosis of AMI must take into consideration other evidence, such as symptoms,

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[3] **Nonstandard abbreviations:** FDA, Food and Drug Administration; hs, high-sensitivity; cTn, cardiac troponin; cTnT, cardiac troponin T; AMI, acute myocardial infarction; ED, emergency department; cTnI, cardiac troponin I.

history, and other tests such as the electrocardiogram. Documentation of a rise and/or fall in biomarkers after serial testing is also essential for the diagnosis of AMI. Is there value in detecting myocardial injury in the absence of AMI? This concept has been explored in a number of clinical venues including heart failure, renal failure, sepsis, pulmonary embolism, cancer chemotherapy, and other situations. It has been consistently shown that an increase in cTn is associated with future adverse cardiac events, suggesting that cardiac injury is never benign (*4*).

Perhaps the most significant medical advance that hs-cTn offers is AMI rule-out. Sandoval et al. (*5*) showed that hs-cTn result below the limit of detection had a 99% negative predictive value. Reichlin et al. (*6*) showed that 60% of patients could be ruled out within 1 h using a δ cTnT cutoff of 3 ng/L with 100% negative predictive value. Similar 1-h rule-out results have been demonstrated with hs-cardiac troponin I (cTnI) assays (*7*) that have not yet been cleared by the FDA. The European Society of Cardiology has recommended a 1-h AMI rule-out protocol based on serial hs-cTn measurements on patients who have no evidence of ischemia on an electrocardiogram, with an expectation of producing a 99% negative predictive value (*8*). Implementation of a 1-h rule-out protocol in the US would have a significant impact on ED overcrowding. However, Pickering et al. (*9*) showed that the clinical sensitivity for hs-cTnT for a 1-h testing protocol was only 97% on 2222 patients studied. This higher missed AMI rate is likely to be unacceptable in the US, since there is a higher rate of malpractice lawsuits in this country (*10*). Roche Diagnostics does not support a 1- or 2-h rule-out protocol in their product literature.

Irrespective of implementing hs-cTnT today or hs-cTnI in the near future, it will be necessary to implement high-sensitivity assays with caution and attention towards prospective communication and education. Optimum implementation of high-sensitivity troponin begins with a discussion among the important stakeholders, such as ED physicians and cardiologists, regarding the expectations of implementing high-sensitivity assays. They must be told that there will be reduced clinical specificity, i.e., increased number of patients with abnormal cTn values who do not have acute ischemic injury. Once implemented, this must be followed by continuing education of medical staff, ideally with examples of patients that they have encountered at their facility. There may be a desire to offer both conventional and high-sensitivity results, but this practice should be discouraged. It doubles the cost of testing, reduces the turnaround time, and likely causes more confusion than value. Use of hs-cTn assays requires more adherence to collecting serial blood collections to adjudicate mildly increased values that would have been within the reference range for cTn assays of conventional sensitivity. It will be poor medical practice to admit all ED patients on the sole basis of a single cTn value above the 99th percentile. Trust in the value of cTn by cardiology will quickly erode if these patients are sent to the cardiac catheterization laboratory and return with a report of clean arteries.

The clearance of hs-cTnT assays will likely result in the use of this test for cardiac risk assessment among asymptomatic patients, not just those who present to the ED with chest pain. Detection of subclinical myocardial damage has been suggested to be an indicator of left ventricular dysfunction. In the Atherosclerosis Risk in Communities Study, patients with cTn values exceeding 3 ng/L (well below the 99th percentile limit of 14 ng/L) had a 2.3-fold risk for mortality and heart failure (*11*). We have discussed the analytical caveats and clinical potential for hs-cTn in this context (*12*). This clinical utility can finally be realized in the US with clearance of the hs-cTnT assay.

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