The State of Cardiac Troponin Assays: Looking Bright and Moving in the Right Direction

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Cardiac troponin assays have evolved substantially over 20 years, owing to the efforts of manufacturers to make them more precise and sensitive. These enhancements have led to high-sensitivity cardiac troponin assays, which ideally would give measureable values above the limit of detection (LoD)4 for 100% of healthy individuals and demonstrate an imprecision (CV) of ≤10% at the 99th percentile. Complete integration and proper use of high-sensitivity cardiac troponin assays into clinical practice will be an important step forward for the diagnosis of myocardial infarction and will allow cardiologists to use cardiac troponin as a prognostic indicator for risk-based outcomes assessment.

As laboratorians, we wish to comment on the recently published “ACCF 2012 Expert Consensus Document on Practical Clinical Considerations in the Implementation of Troponin Elevations” (1). Our purpose is to address 8 analytical issues that we believe have the potential to cause confusion and that therefore deserve clarification. Input from the field of laboratory medicine is important for emphasizing our role as analytical-content experts in the process of strengthening our collaborative relationships with various clinical societies.

Since the initial publications by the National Academy of Clinical Biochemistry (NACB) in 1999 and by the European Society of Cardiology/American College of Cardiology in 2000, when both organizations endorsed cardiac troponin I (cTnI) or cTnT as the preferred biomarker for the detection of myocardial infarction, numerous other organizations have followed suit and promoted the sole use of cardiac troponin in this clinical application. The American College of Cardiology Foundation (ACCF) 2012 Expert Consensus Document (1) summarizes the recently published 2012 Third Universal Definition of Myocardial Infarction by the Global Task Force (2), thus providing some practical recommendations on the use and interpretation of cardiac troponin in clinical practice. The integration and acceptance of cardiac troponin testing over the past 13 years has shown that the measurement of any other cardiac biomarkers for diagnostic use or risk assessment are unnecessary for patients presenting with symptoms suggestive of acute coronary syndromes. The analytical enhancements to cardiac troponin assays have provided clinicians and laboratorians with the needed confidence and ability to use the many automated and point-of-care (POC) assays currently available (3).

Now, we wish to address the 8 analytical issues in question.

1. Interfering substances rarely confound the current contemporary cardiac troponin assays routinely used in clinical practice. Publications regarding the lack of analytical specificity owing to confounders, such as heterophile antibodies and rheumatoid factor, date back to the early 2000s after the initial introduction of cardiac troponin assays. A 2011 publication by Jaffe and colleagues described an immunoreactivity of the Roche high-sensitivity cTnT assay that produced potentially false-positive results in patients with skeletal muscle disease caused by the reexpression of fetal cardiac troponin isoforms. Although this interference is relatively uncommon, it is one that carries potentially serious clinical implications. Cardiac troponin assays remain heterogeneous and highly platform dependent; thus, we agree with the ACCF statement that assays “are not created equal.” Analytical-specificity issues can present particular problems for interpreting serial measurements, in which subtle interferences, such as hemolysis, can easily confound the diagnosis of myocardial infarction. These issues are likely to be magnified with high-sensitivity cardiac troponin assays, and educational efforts should focus on the impact of common preanalytical interferences, such as hemolysis, which is often caused by poor phlebotomy practices in the emergency department. What we have learned with the rapid advances in technology is that the 2007 NACB guidelines are outdated and require revisions to both the analytical and clinical recommendations.

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Received March 7, 2013; accepted March 26, 2013.

Previously published online at DOI: 10.1373/clinchem.2013.203307

4 Nonstandard abbreviations: LoD, limit of detection; NACB, National Academy of Clinical Biochemistry; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ACCF, American College of Cardiology Foundation; POC, point-of-care (assay).
2. Assay of cTnI is not standardized, and it is not likely that it ever will be. The large heterogeneity in capture and detection antibodies used by manufacturers to configure their assays precludes the use of the NIST #2921 reference material to account uniformly for assay-to-assay differences. There will never be an international normalized ratio–like derived calculation or factor for standardizing cTnI assays. Primary users and stakeholders, including clinicians and laboratorians, must be educated about this concept, and they must understand the need to “know your assay” and compare only general trends, not just absolute cardiac troponin concentrations. One of the ACCF report’s coauthors (R.H. Christenson) reported substantial between-assay imprecision in cTnI results after use of the NIST #2129 material, an imprecision that persisted even after mathematical “correction” of concentrations. These data suggested that harmonization of cTnI assays may not be possible (4). Proposing regulatory control is not a solution that will fix standardization or allow harmonization. Instead, it would likely hinder further advances in cTnI assays.

3. As stated in the report of a recent reference interval study that used a common cohort of 526 healthy individuals, 19 different cardiac troponin assays provided 19 different 99th percentile values (5). This finding underscores the need to recognize that assays provide different 99th percentiles, whether the assay is a contemporary assay, a POC assay, or a high-sensitivity one. The ACCF document claims that most POC assays are semiquantitative, when in fact the large majority are quantitative but have lower analytical sensitivity. Cardiac troponin POC testing does provide good diagnostic accuracy, but the POC assays are not as analytically or clinically sensitive as those used in central laboratories. Users need to understand the nuances of their cardiac troponin assay and not presume transferability of the cut points between different assays or laboratories. The influence of age, sex, and ethnicity and the use of cardiac troponin values to detect underlying clinically silent pathologies will continue to challenge our ability to define a presumably healthy population. In this regard, we support the need for an expert consensus opinion that defines what surrogate biomarkers might be useful to delineate “abnormality” so that individuals from the presumably healthy population can be excluded. In addition, there is need to work closely with the US Food and Drug Administration to ensure that manufacturers seeking 510(k) clearance for newly developed assays enroll study individuals in a uniform fashion so that the studies allow true comparisons among assays.

4. Concerning total imprecision of cardiac troponin assays at the 99th percentile, the ACCF document does not mention that assays with CVs between 10% and 20% do not cause false-positive results, as pointed out in Third Universal Definition of Myocardial Infarction document (2). The 2007 NACB document needs updating, because the current evidence-based literature clearly documents that cardiac troponin assays with CVs of up to 20% at the 99th percentile are clinically useable—without appreciable misclassification in diagnostic or risk assessments of outcomes.

5. The concept of “a rising pattern of cardiac troponin” has been in the Global Task Force guidelines since 2000, not 2007 as noted in the ACCF document.

6. The ACCF document advocates for a cardiac troponin δ value of 20%. This point is based on the Global Task Force and NACB documents, but it fails to note the critical caveat that the 20% criterion is appropriate only when a baseline cardiac troponin value is increased. If clinicians base a 20% δ on an initial normal cardiac troponin concentration at baseline to improve diagnostic accuracy, they may be confused by the lack of specificity it provides when they attempt to diagnose acute disease. High-sensitivity assays demonstrate biological variation between 40% and 90% within their reference intervals.

7. How a “high-sensitivity” cardiac troponin assay is defined has yet to be universally accepted. The IFCC Task Force on Clinical Applications of Cardiac Biomarkers recommends that a high-sensitivity cardiac troponin assay be able to measure at least 50% of healthy individuals above the assay’s LoD—not the limit of the blank—along with a CV of ≤10% at the 99th percentile. It is important not to be influenced by the marketed name of an assay but instead to rely on the performance characteristics of the assay after validation and verification. In the absence of assay standardization, users must not be swayed by such notions as “my assay is better than yours,” simply because the assay’s reportable LoD is at a lower concentration. Again, the critical step forward for high-sensitivity assays is to strive to measure 100% of healthy individuals above the LoD, whether it is 0.1 ng/L, 1.0 ng/L, or 10 ng/L.

8. We promote the exclusive use of nanograms per liter as the preferred cardiac troponin SI unit, thereby allowing the use of whole numbers in reporting concentrations.
the US, it is essential that the laboratory community collectively continues to partner with our clinical colleagues and the Food and Drug Administration to streamline this transition and make it successful. We have a new window now to “get it right” on a global scale for high-sensitivity cardiac troponin assays. Let’s not miss the opportunity.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: F.S. Apple, Clinical Chemistry, AACC; A.K. Saenger, Clinical Chemistry, AACC.

Consultant or Advisory Role: F.S. Apple, Instrumentation Laboratory.

Stock Ownership: None declared.

Honoraria: F.S. Apple, Abbott Laboratories and Beckman Coulter.

Research Funding: A.K. Saenger, Roche Diagnostics.

Expert Testimony: None declared.

Patents: None declared.

References


